ELECTROENCEPHALOGRAPHY

AND

CLINICAL NEUROPHYSIOLOGY

AN INTERNATIONAL JOURNAL

(EEG Clin. Neurophysiol.) **NOVEMBER 1956** Volume VIII - Number 4

ELECTROENCEPHALOGRAPHY
AND
CLINICAL NEUROPHYSIOLOGY

AN INTERNATIONAL JOURNAL

Published by

THE INTERNATIONAL FEDERATION OF SOCIETIES
FOR ELECTROENCEPHALOGRAPHY AND CLINICAL
NEUROPHYSIOLOGY, Inc.

PARIS, 1949

REPRINT EDITION

ELSEVIER PUBLISHING COMPANY

AMSTERDAM

ELECTROENCEPHALOGRAPHY
AND
CLINICAL NEUROPHYSIOLOGY
AN INTERNATIONAL JOURNAL

Vol. 8, Number 4 November 1956

MEASUREMENT OF THE DEPTH OF BARBITURATE NARCOSIS [1, 2]

ALEXANDER FORBES, M.D., JEROME K. MERLIS, M.D., GEORG F. HENRIKSEN, M.D.,
SYLVIA BURLEIGH, JEANNETTE H. JIUSTO
and GRACE L. MERLIS

National Veterans Epilepsy Center, Boston V. A. Hospital, Boston,
and The Biological Laboratories, Harvard University,
Cambridge, Massachusetts

(Received for publication: February 15, 1956)

INTRODUCTION

In many studies on the effects of various sensory stimuli on activity in different parts of the brain, the depth of narcosis is a vitally important variable. It is therefore important to be able to choose the depth at which the observations are to be made and to have some sort of quantitative scale by which the narcosis at the time of observation can be measured and recorded for purposes of comparison with other related observations. Such a scale might also find useful clinical applications.

Swank and Foley (1948), working on dogs, studied a number of physiological criteria by which the depth of barbiturate narcosis could be estimated. These included the electroencephalogram (EEG), respiratory volume, the effects of measured concentrations of CO_2 upon respiration, and blood pressure. The changes in these functions were significant and useful, but the nearest they came to a quantitative scale of depth of narcosis was "light, moderate and deep."

In 1949, Forbes, Battista, Chatfield and Garcia, using cats, sought a quantitative measure of the depth of narcosis related to the concentration of the barbiturate (Nembutal) in the blood. To this end, they observed the rate of development of and recovery from narcosis following a large intraperitoneal injection (42 or 48 mg/kg. body weight), as shown by frequency of brain waves, respiratory rate, and blood pressure. Tentative curves of decreasing concentration of the drug in the blood were compared with curves of the "functional mean" — an average of the values of the above-mentioned functions. To test the validity of the presumed curve of drug destruction, analyses of blood samples for Nembutal were made. These showed that the estimates of concentration were of the right order of magnitude.

The number of these evaluation experiments was so small and the variable factors

[1] Aided by a grant from Mr. Edward Mallinckrodt, Jr.

[2] Four preliminary reports have been presented (Forbes *et al.* 1951, 1952, 1953; Forbes and Merlis 1955).

in narcosis so many that only a crude scale of measurement was obtained. In view of the importance of such a scale, it seemed worth while to do a more extensive series of experiments in the hope of finding one more accurate and reliable. This hope has not been realized fully, but much pertinent information has been obtained which may be of value in pointing the way to better measurements of narcosis in the future.

Possible methods of evaluating narcosis can be divided into two main classes: (1) estimates of the concentration of the drug in the blood and active tissues, especially the brain, and (2) objective data revealing the modified activity of the functioning tissues affected by the drug. In the first class are such chemical tests as will measure directly the concentration of the drug, and estimates based on the amount of drug injected and rates of absorption and disappearance. In the second class are measurements of blood pressure, respiratory rate and volume, cortical activity, reflexes, and any other physiological functions that furnish reliable evidence.

Bickford (1950) developed a procedure that affords both a quantitative measure of and a means of automatic regulation of narcosis, by rectifying and integrating the electrical energy derived from the EEG and using that energy on the negative feedback principle to operate the syringe by which the drug is injected into a vein. As the narcosis deepens, the energy of the brain potentials decreases, and this slows the injection rate until a presumably steady state of narcosis is attained. Bickford's contribution furnished a valuable procedure for the pursuit of our quest, and we have followed the lead thus indicated.

TECHNIQUE

The observations were made on 72 cats and one monkey. In three of the early experiments, Pentothal was used, but the narcotic level was too unstable, and all further studies were made with Nembutal (pentobarbital sodium).

The standard procedure was to inject 45 mg/kg. of Nembutal intraperitoneally (i.p.), and after surgical anesthesia was achieved to prepare the animal for recording. In a few experiments, the course of induction was studied by preparing the animal under divinyl ether and ethyl ether and discontinuing the ether inhalation shortly before i.p. injection of Nembutal.

Intravenous (i.v.) injection of Nembutal solution was made through a cannula tied into the brachial vein, kept patent by slow saline drip until injection began. Various automatic injection devices were used. Initially a Bickford (1950) type was constructed, each pulse ("click") from the EEG integrator moving a cog-wheel one step, and each step producing injection of a unit volume of Nembutal solution. Quieter operation was obtained with the Verzeano (1951) modification using a small servomotor, but this was not durable enough for long and repeated use. The final modification, devised by Degelman (1956a), used the stepping relay with a special coupling circuit to avoid the attenuating effect of low shunting impedance, so that it made no difference to the EEG record whether it was connected to the integrator and driving the syringe or not. The system could then be used to record the energy derived from the brain and at the same time be used to drive the syringe. No other change from Bickford's original circuit was made. The response of the integrator to sinusoidal input voltages of constant amplitude was linear through the band-pass of the Grass EEG apparatus.

It was desirable in many experiments to separate the control of narcosis from the recording function of the integrator. To this end, Degelman made a separate driving device to provide constant injection at any desired rate, with the integrator circuit merely recording "clicks" rather than controlling the rate of injection.

With automatically-controlled anesthesia, Nembutal concentrations of 0.6 to 4 mg/cc. were used. For constant-rate injection, at a standard rate of flow from the syringe of 19 cc/hr., dilution of the Nembutal was made to permit injection at rates from 5 to 12 mg/kg/hr. In all experiments, the volume of fluid injected was checked at frequent intervals by reading the calibration on the syringe.

Electroencephalographic (EEG) recording was made through steel phonograph nee-

dles embedded in the skull and leading to a Grass 8-channel inkwriter. The electrodes were placed along the top of the cranium, 3 on a side, about 1.5 cm. apart longitudinally. The first 4 channels were used for "bipolar" recording, the next 2 or 3 for "monopolar" recording, with a nose electrode as reference (fig. 1). The integrator was connected with one of the channels recording from bipolar leads.

Respiration was recorded in some experiments by means of a strain gage pneumotachograph (Degelman 1956b), which provided quantitative recording of tidal volume (fig. 1).

Body temperature was maintained in the early experiments by using hot-water bottles. This proving unsatisfactory, a heating box was constructed, by which body temperature could be held constant within 0.3°C. for hours. Body temperature was measured by a rectal or intramuscular thermometer. In one group of experiments, studies were carried out at different body temperatures, 35° or 39°. The cat was cooled quickly by replacing the heating box with another containing a tray full of ice on a shelf just above the animal.

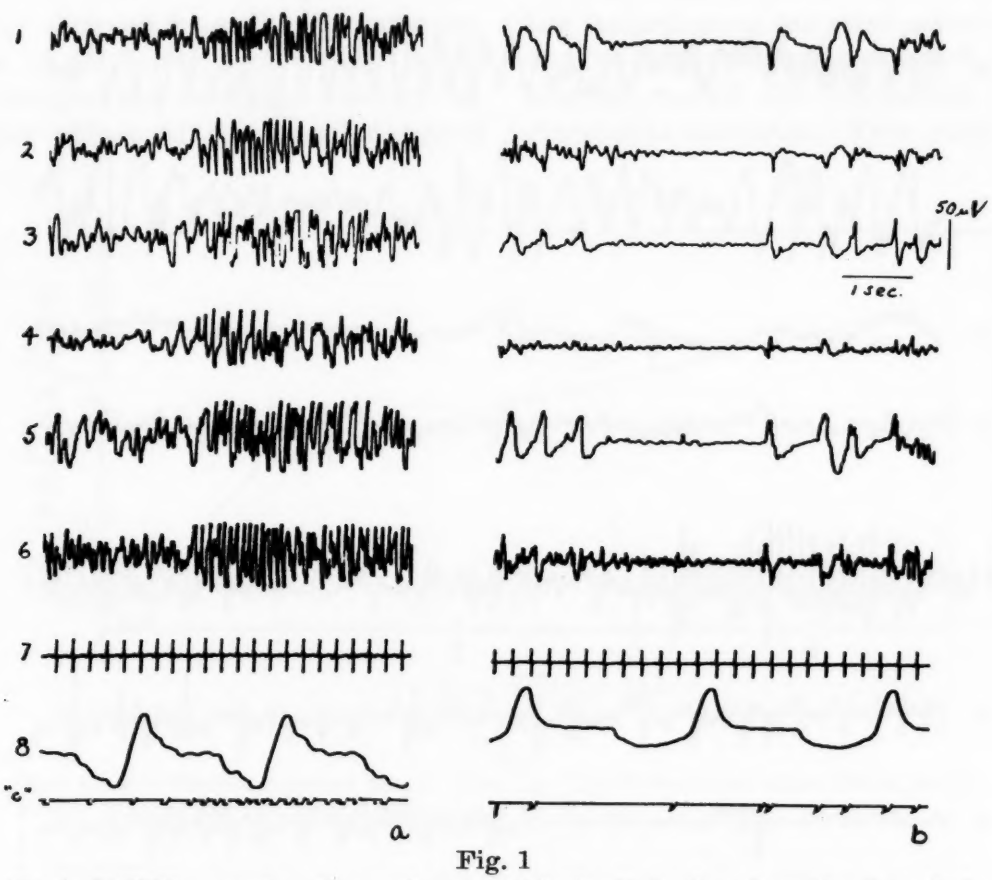


Fig. 1

Typical EEG records. Channels 1-4 "bipolar" leads, channels 5 and 6 "monopolar", channel 7 heart rate, channel 8 respiratory volume. Electrical energy ("clicks") is recorded by signal magnet tracing at bottom. Integrator connected to channel 3. Bias 40 (cf. fig. 13b). Experiment of June 16, 1952; body temp. 37°C. *a*: Light narcosis, 1 hr. after i.p. injection of Nembutal, 45 mg/kg. *b*: Deep narcosis, 9½ hr. after i.p. and nearly 8 hr. after start of i.v. injection; independent syringe drive, average dose rate 5.7 mg/kg/hr. B-w count, *a*: 4.6; *b*: 1.1.

In some experiments, blood for CO_2 and barbiturate analyses was drawn from the femoral artery. In a few it was drawn directly from the heart. Blood CO_2 tension (pCO_2, in mm. Hg.) was calculated by the method of Singer and Hastings (1948) after measurement of CO_2 concentration by the manometric method of Van Slyke or the volumetric

method of Kinoshita *et al.* (1952). Barbiturate concentration was determined by the spectrophotometric method of Walker *et al.* (1948).

In many experiments, tests were made for presence or absence of the flexion reflex at different stages of narcosis by pinching a toe of greatest amplitude. With ½ the maximum, practically no waves attained this value in the deeper stages of narcosis, when significant further decrease could still be observed on the record. The standard adopted consisted of ⅓ of the maximum potential. All waves exceeding this value in a 40-sec. stretch were

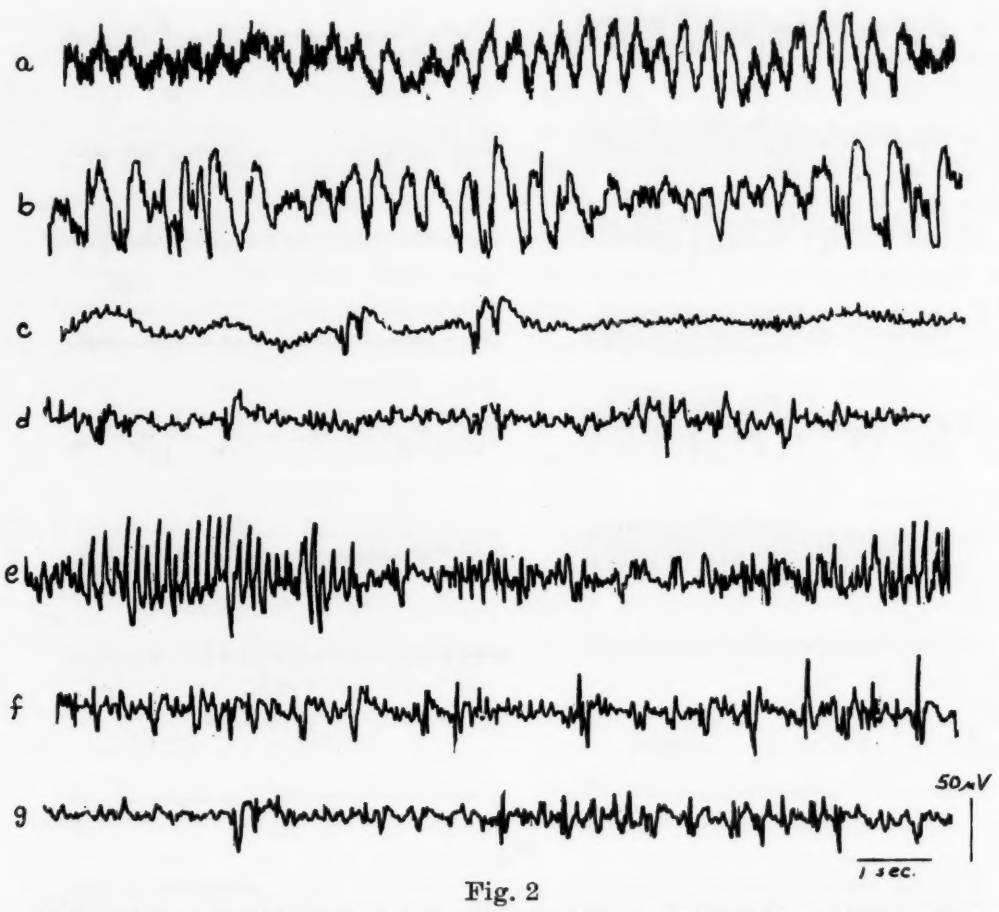


Fig. 2

EEG records showing transition from ether to Nembutal pattern after i.p. injection, 45 mg/kg., and subsequent course before and during i.v. injection. May 6, 1953; body temp. 38°. *a*: Ether pattern, before Nembutal. *b*: Transition to Nembutal pattern, 6½ min. after i.p. injection; b-w count 0.9. *c*: 15 min. after i.p., b-w count 0.25. *d*: 1 hr. after i.p., b-w count 0.6. *e*: 3hr. 20 min. after i.p., b-w count 3.8 .*f*: 3 hr. 45 min. after i.p. and 14 min. after start of i.v.; integrator-controlled, bias 50; initial rate 17 mg/kg/hr.; b-w count 1.3 *g*: 2 hr. 10 min. after start of i.v., dose rate steadied to 6.5 mg/kg/hr.; b-w count 0.7.

pad on the hind foot with large mouse-toothed forceps.

Brain-wave counts. The measure used by Forbes *et al.* (1949), counting all waves exceeding 50 μV., was abandoned because of variation in the voltage of waves from different channels. We adopted an arbitrarily chosen fraction of the voltage of the largest waves at the stage of narcosis when they were counted and the average per second calculated. Hereafter this is designated b-w count. Consistent standards were established and recounts by a given individual as well as check counts by a second observer gave results that almost always agreed within 15 per cent and usually within 5 per cent.

In the deeper stages of narcosis, the waves appeared in bursts, with relative inactivity

between. A 40-sec. stretch might include 4 or 5 such bursts, making the counts vary 20 or 25 per cent on adjacent stretches. Such variations in the count do not signify true differences in depth of narcosis, and in the graphs two or three successive counts have been averaged.

B-w counts have been compared with the "click" counts, by which the integrator measured the energy derived from the brain waves. The grid bias in the integrator circuit could be made to reduce the recorded energy by cutting off the effect of the smaller waves at any desired potential. In some experiments, therefore, the bias was adjusted to cut off at about ⅓ of the potential of the largest waves, to simulate our method of counting brain waves. In other experiments, to find the value giving the closest approximation to the b-w count, the bias was set at several different values periodically throughout the experiment.

titative comparisons bearing on the rates of absorption and elimination of the drug. Such experiments could still be useful for certain purposes, e.g., for relating b-w counts to "click" counts or to analyses of blood Nembutal concentration.

Since the usual surgical preparation precluded recording from the unanesthetized animal, a complete series of b-w counts during the induction of surgical anesthesia could not be obtained. The best approach to this problem was to record the transition from ether to Nembutal narcosis. Two such cases clearly showed the change in pattern described by Derbyshire *et al.* (1936) and Beecher and McDonough (1939). One of these is illustrated in figure 2: the change from the ether pattern to that of Nembutal was complete about 5 min. after ether was withdrawn and Nembutal injected i.p.; the maximum depth of Nembutal narcosis was attained 13 min. after the i.p. injection.

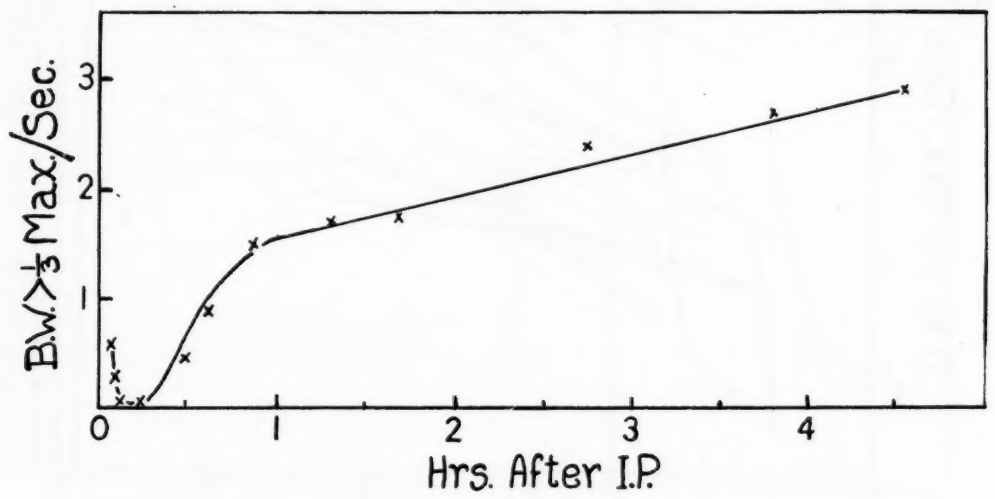


Fig. 3

B-w counts plotted against hours after i.p. injection in an experiment begun under ether. May 13, 1953; body temp. 38.5°.

RESULTS

Course of Narcosis after Standard I.P. Injection

Usually an i.p. injection of 45 mg. Nembutal/kg. induced full surgical anesthesia in from 10 to 15 min. In 11 of the 72 cats, this dose failed to induce narcosis so quickly and a supplemental injection was given. This situation invalidated the experiment for quan-

The high frequency of brain waves under ether renders them unsuitable for quantitative comparison with those under Nembutal. A curve of counts starting from the beginning of the barbiturate pattern is shown in figure 3. This is fairly typical and shows a minimum b-w count from about 7 min. to 15 min. after i.p. Thereafter recovery was at first rapid and then more gradual.

When narcosis was begun by i.p. Nembutal, the first counts were taken between ½ hour and 2 hours after the i.p. injection. Figure 4 is a plot of recovery as indicated by the increase in b-w counts in 30 experiments in which the standard dose (45 mg/kg.) was absorbed at the normal rate and the animal's temperature remained nearly constant.

It will be seen from the vertical scatter that there was wide variation in b-w counts at a given time after the i.p. injection, yet they show a tendency to be grouped not far from the mean, near 3 at 1½ hours. More nearly constant is the slope of the curves which, between 1 and 3 hours, shows an average increase of about 60 per cent. Usually the animals with counts below the average were those whose body temperature was below 38°, which is normal for the cat.

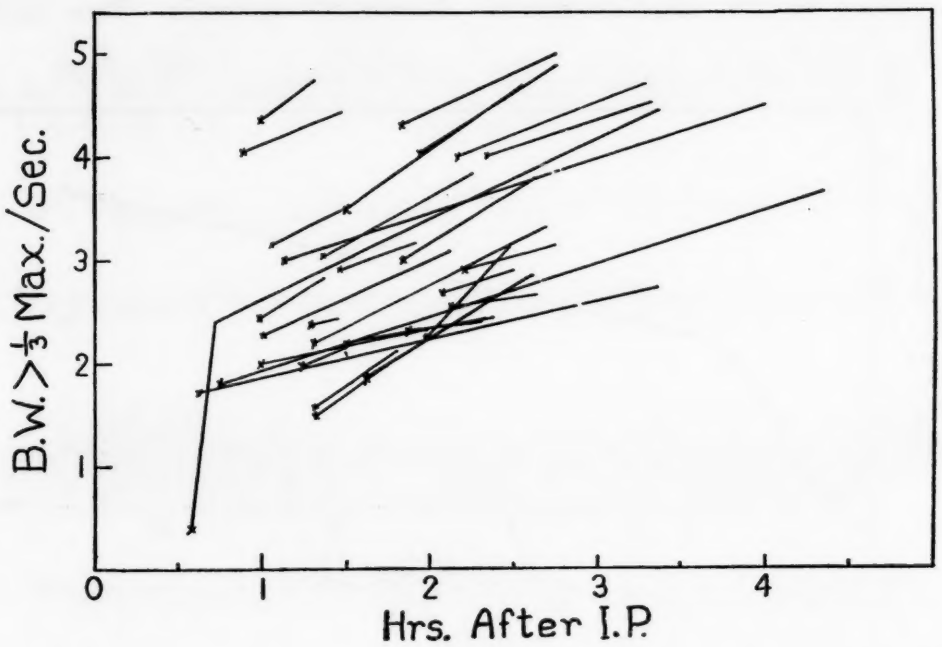


Fig. 4

Plot of b-w counts during recovery from i.p. injection of Nembutal in 30 experiments, showing diversity between animals but tendency to recover at nearly the same rate. For simplicity, all curves except one are plotted as straight lines between two points, early and late in recovery.

The blood Nembutal analyses in six experiments, in which the same standards of procedure were maintained, are shown in figure 5a and are compared with the hypothetical curve of drug disappearance used by Forbes *et al.* (1949, fig. 2 and 3). In two of the experiments, analyses were made at two widely separated intervals after i.p. injection, thus showing the speed of disappearance of the drug (lines). A majority of the 8 analyses agree fairly well with the estimated curve of drug disappearance; two are quite far out of line. A few other analyses in the series were so far out of line as to suggest some gross source of error; these are omitted from the figure. The analyses shown here all indicate concentrations lower than the estimate, but the majority average only 18 per cent less. And the rate of destruction in the two experiments in which it was recorded agrees closely with the estimated rate. The analyses reported by Forbes *et al.* (1949) averaged about 40 per cent more than the estimate. It should be noted that in their experiments the blood was drawn after larger quantities of Nembutal had been injected and the average interval of their samples was much longer after the beginning of narcosis than in the present series.

In figure 5b are shown the analyses of blood drawn from the heart. The quantities

injected were all less than the standard i.p. dose. In the experiment in which injection was into the heart, three successive samples showed a decrease expressed by a smooth curve. Both the i.p. and the i.v. injections were also followed by a decrease along a smooth curve. Evidently the decrease in drug by brain-wave feedback are shown in figure 6. Both show a considerable period of recovery from the i.p. injection before i.v. injection was started. Figure 6a shows the effect of adjusting the electrical controls for a slow injection rate. At the outset, the syringe delivered Nembutal at a rate of 10 mg/kg/hr.,

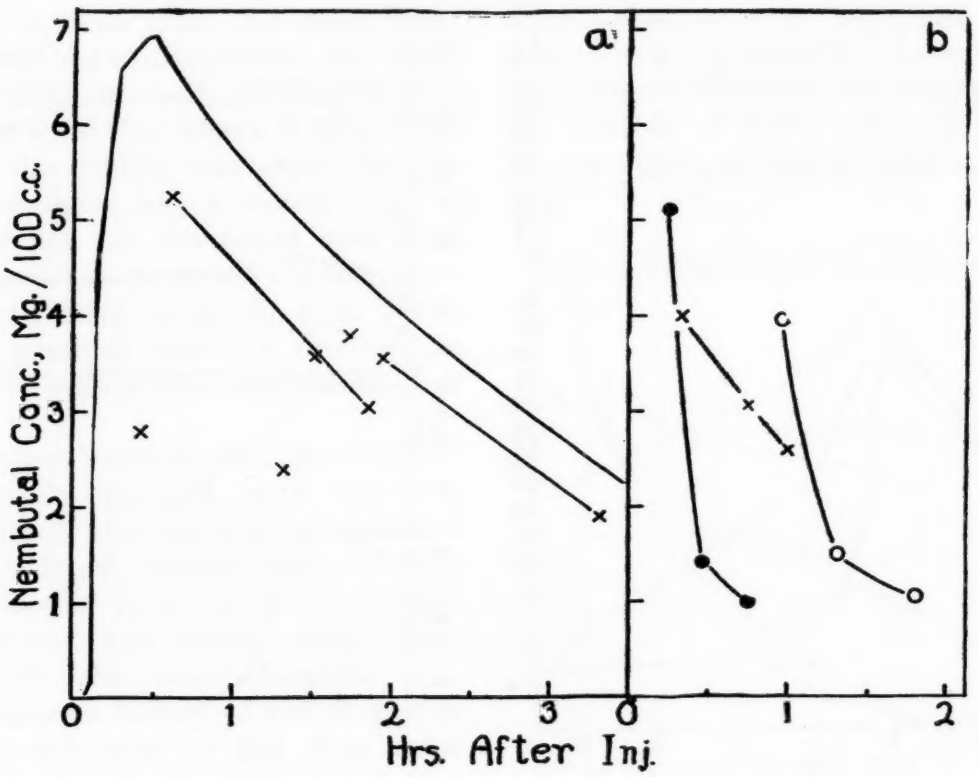


Fig. 5

Analyses of Nembutal concentration in blood at different times after injection. *a*: I.p. injection, 45 mg/kg.; 8 analyses (x) from 6 animals. In 2 of these, two samples drawn more than an hour apart; the lines connecting these points show rate of disappearance of the drug. Above is curve of absorption and elimination assumed by Forbes *et al.* (1949). *b*: Nembutal concentration of cardiac blood after: •, intracardiac injection, 20 mg/kg.; x, i.p. injection, 30 mg/kg.; o, i.v. injection, 30 mg/kg.

concentration is more rapid when injection is directly into the blood stream.

Course of Narcosis with I.V. Injection

Automatically-controlled injection. In the preliminary experiments using the Bickford method of i.v. injection, the rate was varied several times during the experiment by resetting the electrical adjustments (e.g., fig. 11). In the definitive experiments, however, the adjustment was left constant.

Graphs of two typical experiments in which injection was automatically controlled but, in less than 10 min., decreasing cortical activity had begun to reduce this rate, and within an hour it had stabilized at less than 4 mg/kg/hr. For about 4 hours, the "click" rate remained practically constant and the b-w count remained between 3 and 4.

In figure 6b, the controls were set for more rapid injection. For the first 10 min. the syringe delivered the drug at about 28 mg/kg/hr. In 1½ hours the injection rate was stabilized at about 7 mg/kg/hr., and although this rate, as revealed by both the "click" count and the syringe readings, re-

mained nearly steady for 2½ hours, the b-w count continued to decline gradually, suggesting that narcosis was deepening.

The fact that, when the feedback had stabilized the injection rate, this tended to remain constant for a fairly long time, often

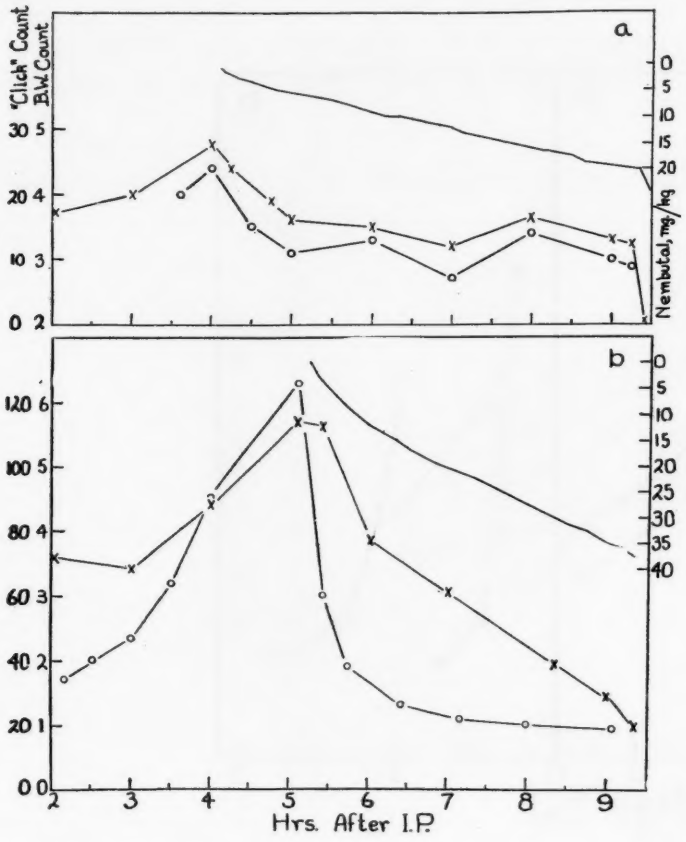


Fig. 6

Graphic records of 2 experiments in which i.v. injection was regulated by integrator feedback. *a*: Integrator adjusted for light narcosis; bias 60; June 10, 1953. *b*: Adjusted for deep narcosis; bias 45; May 27, 1953. In both, body temp. steady at 38°. In this and figures 7, 9, 10 and 11, the upper line depicts the quantity of Nembutal injected, ordinates reading downward, the slope showing the dose rate. x, B-w counts; o, "click" counts.

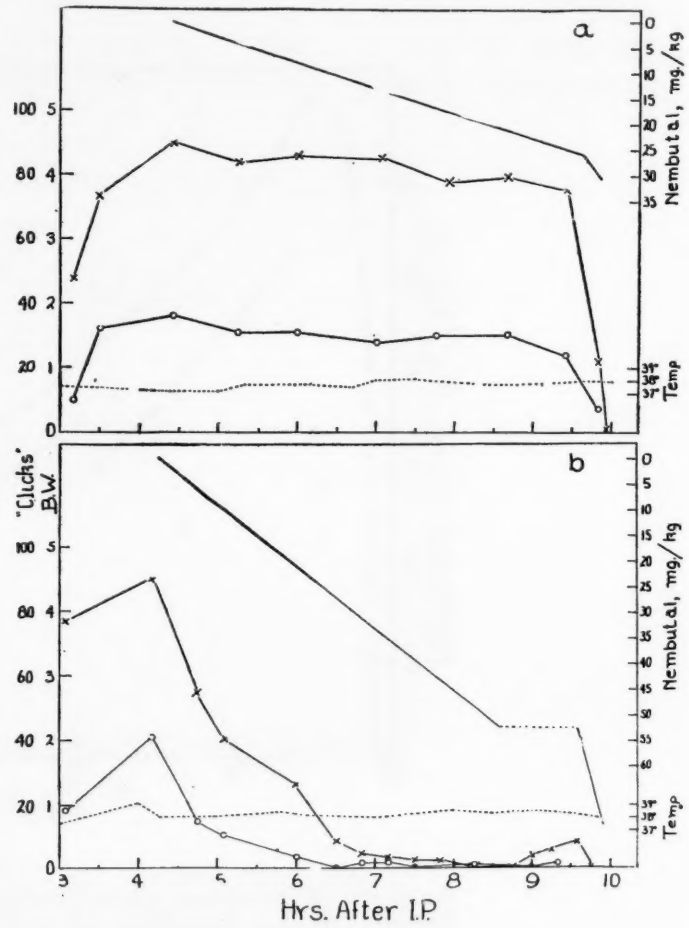


Fig. 7

Two experiments with constant-rate i.v. injection. *a*: 5 mg/kg/hr.; bias 76; Feb. 25, 1953. *b*: 12 mg/kg/hr.; bias 60; April 1, 1953. Body temp. represented by broken line at bottom.

more than an hour, suggested that a constant injection rate might suffice to maintain a constant depth of narcosis. To determine the feasibility of simplifying the regulation and measurement of narcosis by using a constant injection rate, a large number of experiments were made with independently-controlled injection.

Constant injection rate. Several different experimental procedures were adopted. In many instances, the injection rate was kept constant throughout the experiment. In others, injection was discontinued for a time and then resumed at the same rate. In still others, the injection rate was abruptly changed from a low to a high rate, then back to the low rate again. In all of these experiments, the animal's temperature was maintained as constant as possible. Finally, the effect of temperature was tested.

When the i.v. injection was kept at a constant rate from the start by means of the independently-controlled syringe drive, the injection was begun at times varying from 1 hr. 22 min. to 3 hr. 42 min. after the i.p. injection (many of the experiments in fig. 4). The "click" counts, although no longer a measure of injection rate, were recorded to learn how closely they correlated with b-w counts and how reliable a measure of narcosis

they might be. The periods of injection ranged from 3½ to 7 hr., and the Nembutal injection varied from 5 to 12 mg/kg/hr.

Figure 7 shows graphs of two typical experiments in which constant-rate i.v. injection began after a long period of recovery. In 7a, the i.v. was at the minimum rate, 5 mg/kg/hr., in 7b it was 12. In each experiment, the b-w counts are compared with "click" counts derived from the same channel. At the lower rate of injection the brain activity, after about an hour, stabilized at a nearly constant level for about 3 hr. With 12 mg/kg/hr., the decline was rapid for the first hour, then there was a slower rate of decline, but by 3½ hr. the count was close to zero. This condition persisted till the injection was stopped after 4 hr. 20 min. Then began a slow, gradual recovery during the next hour, after which the experiment was terminated.

In both of these experiments, the "click" counts ran closely parallel with the b-w counts. In general, this correlation obtained between the electrical energy and the b-w counts in the channel from which this energy was integrated and was visibly closer than with counts made from other channels.

Figure 8 presents a family of curves giving average results for each of the dose rates employed. These were selected from a larger number of such experiments; all animals receiving more than one i.p. dose were eliminated, as were animals whose body temperature varied significantly during the experiment. The animals used displayed, at the beginning of i.v. injection, a b-w count of 3.5 to 4.5. The initial counts were all adjusted to a common starting point and the curves proportionately corrected. This figure therefore portrays somewhat more clearly than the one published by Forbes *et al.* (1953) the rates of decline of b-w count with different Nembutal doses. The crossing of two pairs of curves after several hours of injection appears to reflect differences in individual responses.

In general, 5 mg/kg/hr. maintained a nearly constant level of narcosis for several hours. At 6 mg., the level of narcosis dropped slightly for several hours and then became stabilized. In both cases, the count began to fall off more steeply after 5 to 6 hr. (fig. 7a). With injection rates of 7 mg. or more, there was regularly a progressive decline, although sometimes the rate of decline slowed for a while. And with rates as high as 10 or 12 mg., the decline proceeded fairly rapidly to the point of cortical quiescence, in which long periods occurred without any measurable waves.

That the ability to destroy the drug becomes progressively impaired was demonstrated in a few experiments in which a fairly high rate of injection was interposed between two periods of lower rate. Figure 9 shows the course of narcosis in such an animal. For

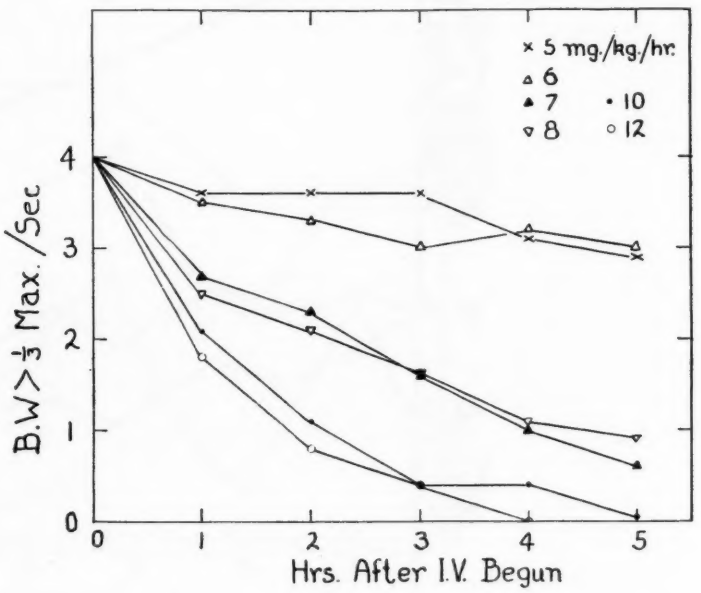


Fig. 8

Average rates of decline of b-w count at 6 dose rates of Nembutal, from 5 to 12 mg/kg/hr. The beginning of i.v. injection varied from 2 to 4 hr. after i.p. injection. Curves adjusted to start from the same point, the better to show the divergent slopes. Body temp. constant at 38° in all cases. Averages from 2 animals at dose rate 5, 2 at rate 6, 2 at rate 7, 3 at rate 8, 3 at rate 10, and 2 at rate 12.

3 hr., the i.v. injection was maintained at 6.3 mg/kg/hr., and during that time the b-w counts became fairly steady at 2. Then the rate was increased to 12.3 mg., and the b-w count rapidly decreased to a level of 0.9, indicating deep narcosis. After one hour, the injection rate was restored to 6.3 mg. The return to the lower rate did not raise the b-w count; instead it became stabilized at the lower level. This effect was regularly found in all experiments of this type.

In a few experiments, the i.v. injection ran at a fairly high constant rate for about 2 hr. and was then discontinued for a period which sufficed for recovery to about the same b-w count as that immediately preceding the i.v. injection. When injection was resumed, the b-w count declined much more rapidly than during the first injection. This again points to the cumulative effect of prolonged or repeated injections.

Temperature. In one experiment (June, 1952), the weather was abnormally hot and the temperature in the laboratory rose to 40°C. It was impossible to bring the cat's body temperature down to the normal range, 38°, and narcosis remained unusually light in relation to the dose administered. This observation led us to surmise that high body temperature accelerated the disappearance of Nembutal. To test this point, we did a variety of experiments to study the effects of high and of low body temperature on the course of narcosis. These showed that at 35° the decline of cortical activity during injection was more rapid and, on cessation of injection, the recovery was somewhat slower than at 39°.

One such experiment is illustrated in figure 10. The cat's temperature was brought down to 35° at the time i.v. injection was begun (12 mg/kg/hr.). .This injection was continued for 30 min., at which time the b-w count was down to 1. The recovery curve was followed for nearly 2 hr. at this temperature. Then the body temperature was increased to 39°, at which time i.v. injection was resumed at the same rate and continued till the "click" counts showed that the brain activity had fallen to the same level as before. At this higher temperature the time required was 40 min. Injection was then stopped; the recovery was more rapid than at the lower temperature, in spite of the fact that recovery from a second injection had regularly been found to be slower than that from the first when the temperature was constant.

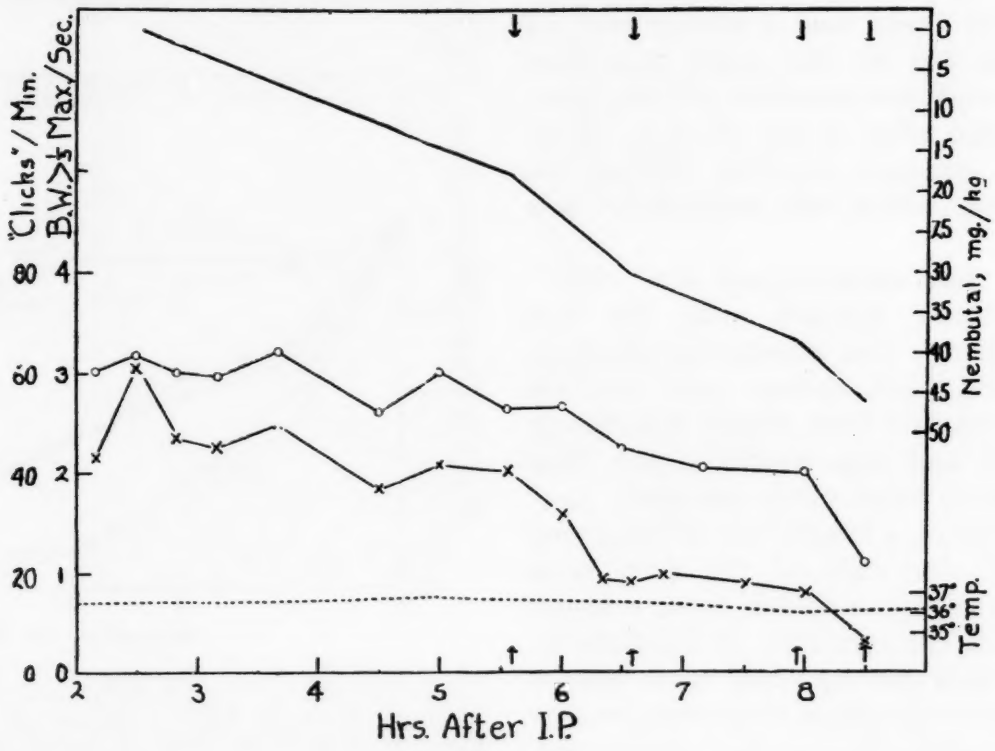


Fig. 9

Experiment with constant-rate injection, low rate interrupted by 1 hr. at high rate. Bias 41; Nov. 30, 1951. Arrows: times when injection rate changed.

Such experiments showed that rather small changes in temperature significantly affected the rate of Nembutal destruction and thus

altered the course of narcosis at a given injection rate. Thereafter especial care was taken to keep the temperature as nearly constant as possible, close to 38°, and it is such experiments that have been used for illustration above (fig. 6 to 8).

Concentration of Nembutal in the Blood

Fifty-five analyses for blood Nembutal concentration from 16 experiments have been compared with the b-w counts at the same time. Several analyses showed poor correlation with the amount of Nembutal which could reasonably be expected on the basis of the amount administered. In some, clotting of blood in the sample was a patent source of gross error. But some of the analyses, in which no clotting was noted, were so far out of line with other indications that more obscure sources of error probably invalidated them.

In some experiments, several successive samples showed satisfactory correlation with the quantities of Nembutal injected. One of these is illustrated in detail in figure 11. In this case, i.v. injection was begun 83 min. after the standard i.p. injection and was controlled by Bickford feedback, set at an initial injection rate of about 25 mg/kg/hr. In 40 min. this had induced deep narcosis and injection was stopped. Nembutal concentration by analysis increased during this i.v. injection from 2.4 to 4.3 mg/100 cc. blood. Two hours without injection brought the concentration down to 2.7 mg., and the b-w count had risen to more than half that found before the beginning of i.v. injection. Resumption

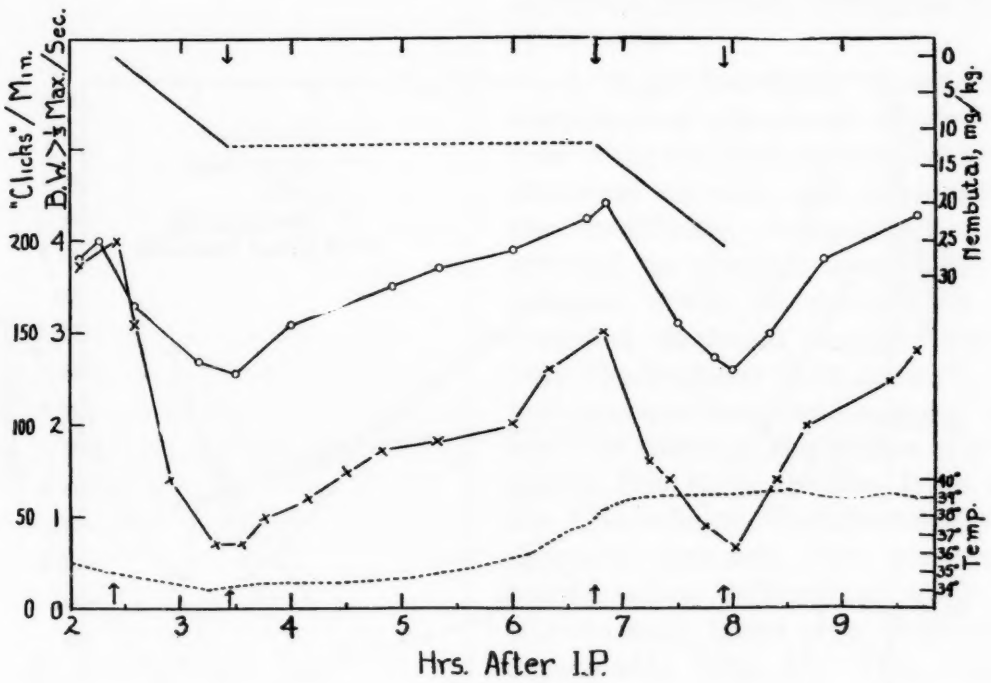


Fig. 10

Experiment comparing response to Nembutal at two different body temperatures in the same animal. I.v. injection rate same both times, second injection stopped when "click" count (o) the same as at first cessation. Arrows: times when injection started or stopped. Bias 40; Jan. 28, 1953.

of i.v. injection at a lower rate then caused increase in blood Nembutal concentration and a corresponding decline in cortical activity.

From six experiments in which the analyses showed an orderly relation to the amount of drug injected, b-w counts have been plotted against blood Nembutal concentration (fig. 12). The count in each case was made on the records taken just before and after the blood sample was drawn. It is evident that there is considerable divergence in the relation of b-w count to Nembutal concentration in different cats. On the aver-

age, however, judging from all of the records, when the blood level was 2 mg/100 cc. the b-w count was 2.0 to 3.8, when 3 mg., 1.4 to 3.0, when 4 mg., 0.6 to 1.9, and when 5 mg., 0.2 to 1.0. Inspection of the records suggests also that there was a tendency for the cortical activity to be lower in proportion to the measured Nembutal concentration when there had been prolonged narcosis than in the early hours of drug administration.

CO_2 Tension

In view of the tendency of barbiturate narcosis to induce accumulation of CO_2 in the tissues (Beecher and Moyer 1941), thus causing a vicious circle in susceptibility to the drug (Forbes *et al.* 1949, p. 148), comparison of CO_2 tension in the blood at the beginning and end of typical experiments is important. A fairly average case is shown in figure 11. In this instance, CO_2 tension had increased somewhat at the end of the experiment when narcosis had been pushed to a very deep stage. In a few experiments, the increase in CO_2 tension was more marked. In others there was no increase, or a slight decrease, even in animals in which large doses had increased the Nembutal concentration in the blood to a high level and cortical activity was profoundly depressed. It is clear then that although increased CO_2 tension may have added to the depressing effect of Nembutal in some cases, in others the decline in cortical activity after prolonged narcosis cannot be explained by this influence.

Flexion Reflex

Presence or absence of the flexion reflex was recorded at intervals in 25 of the experiments. The results showed more variability in comparison to the depth of narcosis as measured by cortical activity than can be ascribed to the crudity of the method of evoking and recording the reflex. For example, in one cat, the flexion reflex was absent when the b-w count exceeded 5. In another, it was present when the count was only 1.5; in the latter case, spontaneous movement showed that narcosis was not deep, so that the b-w count was deceptively low. In gen-

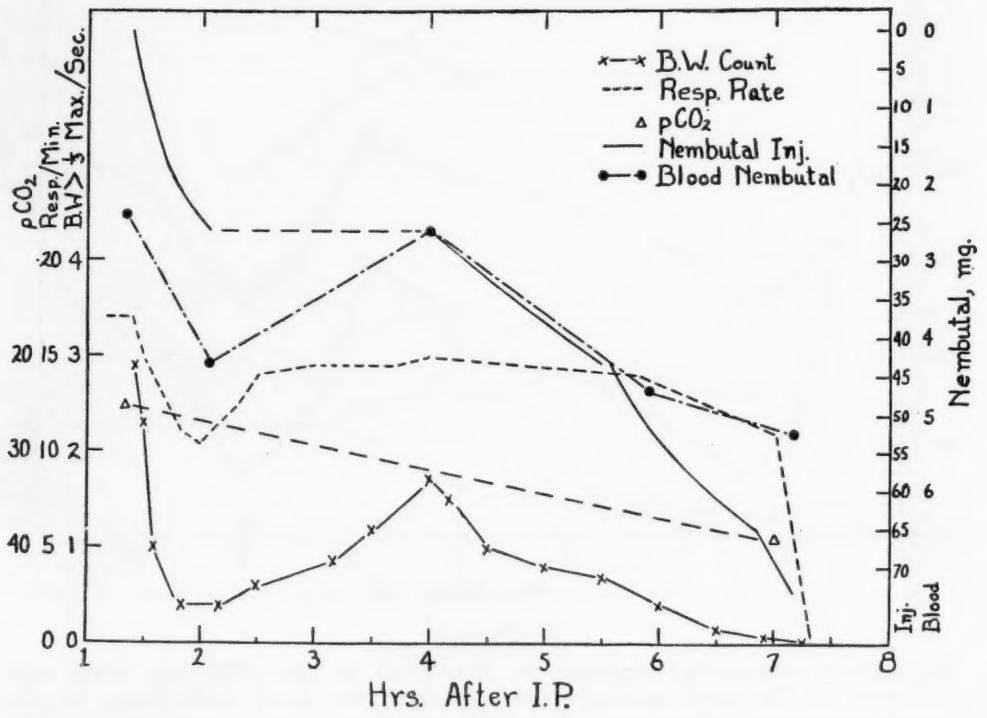


Fig. 11

Experiment with integrator-controlled i.v. injection, showing injection rate, blood analyses for Nembutal and pCO_2, respiratory rate and b-w count. Body temp. 35-36°; May 17, 1951.

eral, the results were fairly consistent in showing disappearance of the flexion reflex as the b-w count fell between 4 and 2.5. Three experiments in which blood analyses were made at about the time the reflex disappeared showed concentrations ranging between 3.1 and 2.7 mg. Nembutal/100 cc. blood.

Respiration

In the few experiments in which respiratory minute volume was measured in addition to respiratory rate, curves were plotted to determine how closely they correlated. When respiration was accelerated by thermal stimulation, the curves diverged, and respiratory volume did not increase in proportion to the increase in rate. Otherwise the agreement between the two curves was so close that no significant information could be gained by the laborious measurement of volume.

Respiratory rate decreased with large increases in depth of narcosis but was a much less sensitive indicator than b-w activity (fig. 11). Often respiratory rate remained virtually constant while deepening narcosis caused a steady decline in b-w count, and this constant rate might persist until a very deep stage of narcosis, before abruptly decreasing and ceasing.

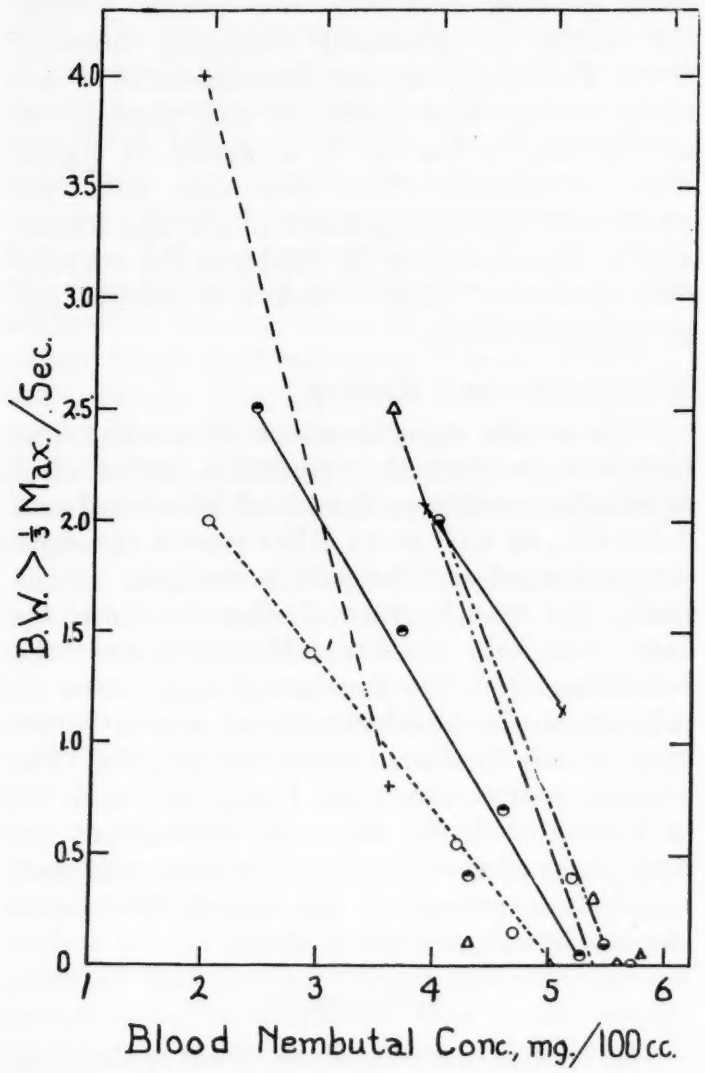


Fig. 12

B-w counts plotted against blood Nembutal concentration, 6 experiments.

Rectified Electrical Energy as a Measure of Narcosis

A hope has been entertained that, by standardized placement of electrodes, in relation to the cerebral cortex and by standardized electrical circuits and constants throughout the rectifying, integrating and recording systems, an absolute measure of the depth of narcosis could be established in terms of recorded electrical energy (Verzeano 1951). Our observations show a fairly close correlation between recorded energy (''click'' count) and b-w count in the course of a single experiment, but it is obvious from inspection of the EEG records that the energy output from adjacent channels, even when symmetrically placed, often differed so much that a quantitative scale based on a single channel is not dependable (fig. 1). This could be shown also by switching the integrator from one channel to another during an experiment. Yet generally records from adjacent channels were so similar that a fairly good approximation might be obtained by recorded electrical energy if adequate constancy in the electrical system could be obtained.

Inspection of the graphs of single experiments in which the grid bias (40 to 45 on the dial) permitted a high ''click'' rate (fig. 6b, 9, 10) shows that, though there is almost always a consistent correlation between ''click'' and b-w counts, the relation is not linear. As the b-w frequency fell, the ''click'' count fell too, but proportionately less. To analyze this relation, in five successive experiments the recording system was standardized with a constant value of the grid bias (40 on the dial); a calibrating 6-V. A.C. input was

introduced and the sensitivity of the integrating circuit was adjusted to respond to this input with a standard "click" count of 112 ± 4/min. In figure 13a the ratio of "clicks"/sec. to b-w count, as ordinates, is plotted against b-w frequency at several stages of narcosis. In every experiment, the ratio of "clicks" to brain waves increased as the

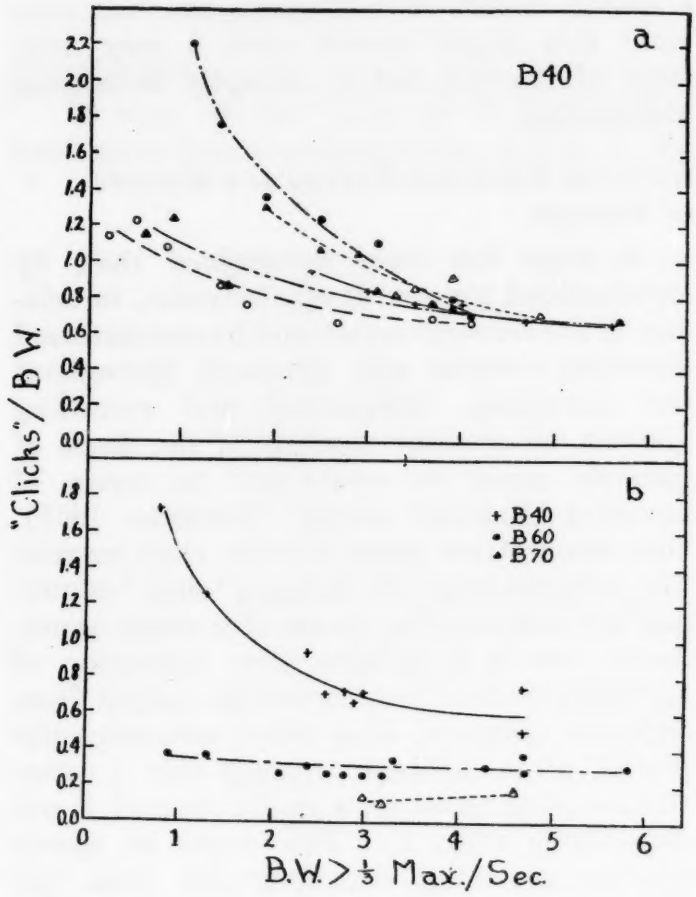


Fig. 13

Ratio of integrator "clicks"/sec. to b-w count against b-w count. *a*: Graphs from 5 experiments with bias 40 on dial. Sensitivity 80 to 85, adjusted for standard "click" rate on 6-V. calibration. Experiments in Jan. and Feb., 1953. *b*: Similar graphs from one experiment, with 3 values of bias; sensitivity 80. March, 1953.

frequency decreased. In each experiment, there was a moderate scattering of points. Between different experiments there was wider divergence, especially when activity was greatly reduced. In the more active states, the ratio was dominantly close to a value of 0.7.

In another three experiments, the grid bias was adjusted so that only voltages exceeding approximately ⅓ maximum were integrated. The maximum voltage was established when the EEG showed that recovery from the i.p. injection had progressed to the stage of maximum amplitude of cortical waves (fig. 1a, 2e). Plotting the "click"-to-b-w ratios in these three experiments showed that they were nearly constant at all levels of narcosis.

In six other experiments, the integrator sensitivity was kept constant but the grid bias was changed frequently for about a minute at a time, so that the "click" counts at bias dial settings of 40, 50, 60 and 70 could be compared with b-w counts during the course of gradually changing narcosis level. The result for one experiment in which many counts were made at bias settings 40 and 60 and a few at 70 is shown in figure 13b. It appears from this that with the particular dial arrangement in our apparatus, a grid bias setting at 60 rendered the correlation between "click" and b-w counts approximately linear.

Observations on a Monkey

The single experiment on a monkey was complete, in that it included a series of 5 satisfactory analyses for blood Nembutal and 2 for CO_2 as well as an EEG record throughout prolonged and deepening narcosis. In the main, the results were similar to those for cats. The only notable differences were the following: (1) the b-w count was lower in relation to the blood Nembutal concentration than in any similar experiment on cats. The average count was 2 at 1 mg/100, and 0.7 at 1.5 mg. (cf. fig. 12); (2) throughout the deep stage of narcosis, in which long quiescent intervals appeared in the record, the waves came in bursts, instead of singly.

DISCUSSION

In view of these findings, what is the most practical method of adjusting and evaluating the depth of barbiturate narcosis ?

Drug Concentration

Chemical analysis of Nembutal concentration in the blood by the method of Walker *et al.* (1948) has proved valuable in this research and the previous one (Forbes *et al.* 1949) in showing the approximate concentrations corresponding to various stages of nar-

cosis, as shown by physiological evidence. Thus it has established a quantitative basis for measurement, although a crude one. Recently, another method of analysis has been developed by Brodie *et al.* (1953) which might prove more reliable. Such analysis, however, is not suitable for use in the course of an experiment. Aside from the delay and inconvenience of drawing samples of arterial blood, the result of analysis is not available for many hours.

The rate of intravenous injection of Nembutal determines the depth of resulting narcosis (fig. 8). Injection at 5 or 6 mg/kg/hr. establishes a fairly constant but light level of narcosis, corresponding roughly to 2 mg. Nembutal/100 cc. blood at the 6 mg. dose. This level can usually be maintained for 3 or 4 hr., which is long enough for most experiments. Yet the susceptibility to the drug varies in individual animals enough to render evaluation on the basis of injection rate a rather rough approximation at best. Furthermore, when the injection rate exceeds 6 mg/kg/hr., the narcosis, as measured by physiological signs, increases progressively, due apparently to increasing failure to destroy the drug.

The relation of blood CO_2 tension to barbiturate action is important. It has been shown that various narcotics, including barbiturates, reduce sensitivity of the respiratory center to CO_2, and the resulting accumulation of CO_2 augments the narcosis (Beecher and Moyer 1941; Dripps and Severinghaus 1955). Our results indicate that while this vicious circle may contribute to the progressive decline of brain activity during continued injection of the drug, it is not the principal cause of that decline. Some other factor or factors must be operative. One factor might be fatigue of liver function (Papper and Ngai 1954), causing impairment of its capacity to break down the barbiturate. Dr. Helen W. Deane has suggested that addition of glucose to the infusion might delay this loss of power to destroy the drug.

Kahn (1950) reports that after i.p. injection, C^{14}-labeled Nembutal regularly shows less concentration in brain tissue than in blood. Destruction of Nembutal occurs chiefly in liver and kidney. The degree to which the drug combines with proteins and the details of its action on cell membranes remain unknown, however. Until such information is available, we must rely on physiological rather than chemical findings in our efforts to measure narcosis.

Another factor in the depth of narcosis is body temperature, which appears to affect the rate of destruction of the drug (fig. 10). In addition to this effect, changes in temperature may directly alter the brain-wave pattern (Gaenshirt *et al.* 1954). Related to our data on temperature effects are unpublished observations, reported to us by Dr. Kenneth Rawson, of the Harvard Biology Department, that white-footed mice with a body temperature of 15°C. required only half as much Nembutal to narcotize them to the point of muscular relaxation as they did at 37°.

Arañez and Forteza (1955) reported a study of narcosis with thialbarbitone sodium (Kemithal) in dogs, in which they compared the effects of various intravenous doses from 44 to 100 mg/kg. They found a marked prolongation of the periods of anesthesia and recovery as the dose increased. The transition from the "therapeutic" dose to the "toxic" dose (about 80 mg/kg.) was marked by a very great prolongation of the recovery period. These observations appear to represent the extreme condition of impaired ability of the body to destroy and eliminate the drug, an effect already appreciable in our experiments when as little as 6 mg/kg/hr. was continued for more than 5 hr.

A practical result of the progressive deepening of narcosis at a constant injection rate is the conclusion that when the Bickford feedback mechanism is employed and is adjusted to stabilize at a rate above 6 mg/kg/hr., this will not maintain a strictly constant level for more than a limited time. As the ability to metabolize the narcotic decreases, the narcosis will tend to become deeper at the injection rate at which stabilization had occurred. The injection rate will automatically slow down, setting a new stabilization level, but again the cycle will recur. Eventually, unless the apparatus is set to give zero injection rate, narcosis inevitably will deepen.

It is probable that narcosis can be better stabilized by adjusting the grid bias of the

integrator to cut off all effective action of the system at a small fraction (e.g., 30 per cent) of the maximum potential of the cortical waves. In that case, injection would cease altogether when no waves exceeded that voltage. Cessation of injection would permit recovery until waves of the critical magnitude reappeared, and stability of this level might be maintained for a long time.

Physiological Data

The best measures we have found for depth of narcosis appear to be physiological criteria, rather than estimates of concentration of drug in the tissues, either by analysis or by empirical formulae. Respiratory rate is the simplest and least expensive method, for it requires no intricate recording instruments. As already noted, however, it is only good for major changes in narcosis and not nearly so sensitive as brain activity in recording minor fluctuations. Indeed, it may remain nearly constant while the b-w count is decreasing from a fairly high frequency to nearly complete extinction (fig. 11).

Reflexes, such as the flexion reflex, are also good indicators within limits. They correlate roughly, though not accurately, with brain activity, but they disappear completely in the deeper stages of narcosis. Important changes of level can be distinguished by brain waves after the flexion reflex has wholly disappeared.

Our experience indicates that brain waves (EEG) are the best index of depth of narcosis. Comparable conclusions have been drawn by Kiersey *et al.* (1951), who described 5 stages of barbiturate narcosis in humans, and by Clowes *et al.* (1953), who distinguished 6 stages. The degree of activity the EEG evinces may be measured in various ways. We are inclined to consider the method used here, counting all waves exceeding a chosen fraction (⅓) of the voltage of the biggest waves during moderate narcosis, as reliable a measure as any. This, of course, requires EEG recording apparatus.

The pulses of electrical energy (''clicks'') recorded by the Bickford (1950) integrating system afford a more objective method and the ''clicks'' can be counted much more quickly and reliably than brain waves, and indeed while the record is being taken. On the other hand, variation of energy derived from different channels renders the ''click'' count invalid as an absolute measure of narcosis, however reliable it may be as a relative measure in the course of a single experiment. Proper adjustment of the grid bias to minimize the recording of energy due to waves of less than some chosen voltage improves the correlation between ''click'' and b-w counts. By careful standardization of the electrical adjustments and by connecting the integrating circuit to a channel that shows a typical EEG record of average amplitude, the ''click'' count can be made a convenient measure of narcosis, nearly as dependable as a good b-w count.[1]

In spite of the many variables involved and the rather wide differences between animals and indeed between channels in a single record, b-w counts, ''click'' counts and the flexion reflex are roughly related to Nembutal concentration in the blood. A scale of such average values is shown in table I. Precision in this is not claimed, and standard deviations have not been estimated, but still the approximation may be valuable.

TABLE I

Average relation of b-w count, ''click'' count and flexion reflex to blood Nembutal concentration.

Blood Nembutal Conc., mg./100 cc.	B.W.>⅓ Max. / Sec.	''Clicks''/Sec., B. 60, S. 80*	Flexion Reflex
2.0	3.0	1.0	+
3.0	2.0	0.7	—
4.0	1.0	0.3	—
5.0	0.5	0.2	—

* B, grid bias and S, sensitivity settings of integrator.

Proposed Procedure for Constant Narcosis

A convenient procedure for adjusting the depth of narcosis to a desired level and main-

[1] It is important to have all switches in the recording apparatus at the same standard settings in order to make results comparable between experiments. Neglect of this precaution can lead to serious discrepancies. For example, a change of gain in the preamplifier can be compensated by a change of gain in the power amplifier, but if the integrator is connected to the output of the preamplifier, there will be a discrepancy between outputs as measured by the integrator and inkwriter.

taining it so for the duration of an experiment would be as follows: the animal should receive at the outset a standard i.p. dose of barbiturate (between 42 and 48 mg/kg. in the case of Nembutal). Electrodes should be connected with a reliable EEG recorder in which all adjustments are set at standard values, maintained constant thereafter. A 2-channel recorder would suffice. An integrating circuit containing the features described by Bickford (1950), as modified by Degelman (1956a), should be connected with one channel at the input of the power amplifier and should be arranged to record pulses of energy by means of a signal magnet or through one of the regular channel inkwriters. The grid bias in the integrator should be adjusted to cut off responses to waves below a voltage chosen as affording good correlation between "click" counts and b-w counts made according to a convenient standard. The correlation should be as nearly linear as possible.

When recovery from the i.p. injection approaches the point at which the integrator shows the maximum energy output, usually after about one hour, the sensitivity control can be adjusted to give a conveniently large number of "clicks" per minute, e.g. 100. This adjustment should then remain unchanged. Intravenous injection should then be made with an adjustable syringe drive until the desired level of narcosis is attained. If fairly deep narcosis is desired, this can be reached quickly by starting the injection at 10 or 12 mg/kg/hr. When the desired stage is attained, judged be EEG pattern and "click" count, the syringe drive is adjusted to hold the "click" frequency as nearly constant as possible. If the frequency remains steady, it will indicate a constant level of narcosis, provided body temperature is kept constant, close to normal, and the cortical activity is not significantly disturbed by sensory stimuli. If stimuli are an essential part of the experiment, a quiet interval of 4 or 5 min. between periods of stimulation will probably suffice to afford an undisturbed EEG, in which "click" counts can serve as a check on the constancy of narcotic level.

SUMMARY

1. Depth of narcosis is an important variable in the study of brain function. A quantitative scale for its measurement with means of regulation would be of value in physiology and clinical practice.

2. In many cats under Nembutal, we have used electroencephalography, respiration, the flexion reflex and analysis of blood for drug concentration as standards of measurement.

3. Starting with intraperitoneal injection of a standard dose of Nembutal, recovery was recorded. In a few cases, the initial surgery was done under ether and the EEG then recorded induction of narcosis by the i.p. injection. Thereafter narcosis was continued by intravenous injection, sometimes regulated by the Bickford feedback control, sometimes by an independent electric drive.

4. The EEG proved the best indicator of the depth of narcosis. Two methods of EEG measurement were used: (1) the frequency of waves exceeding ⅓ of the maximum voltage; (2) the electrical energy derived from the EEG, rectified and integrated by Bickford's (1950) method. By proper choice of grid bias, the recorded energy could be made to correlate closely with the brain-wave count. As an absolute measure of narcosis, the brain-wave count appeared more reliable than the energy record.

5. Blood analyses showed roughly the rate of disappearance of Nembutal after the standard i.p. dose (fig. 5). Brain-wave counts showed the corresponding recovery of function (fig. 4). There was wide variation in the brain-wave counts in different animals, but the rate of recovery was fairly uniform.

6. The dose rate of i.v. injection determined the resulting depth of narcosis, which remained nearly constant for several hours if the rate was less than 6 mg/kg/hr. At higher rates, the narcosis grew progressively deeper (fig. 8). The failure to stabilize under these conditions suggests the loss of ability of the body to destroy the drug. Increasing CO_2 tension in the blood may augment narcosis, but in several experiments loss of ability to destroy the drug occurred without increase in CO_2 tension.

7. The influence of Nembutal was greatly affected by even small changes in body temperature (fig. 10). Therefore, accurate temp-

erature regulation is essential in the standardization of narcosis.

8. The vigor of the flexion reflex indicated the depth of narcosis in the lighter stages but was imperfectly correlated with brain-wave activity and disappeared at a moderate depth of narcosis. Similarly, respiratory rate was an insensitive measure of narcosis.

9. A single experiment on a monkey showed greater susceptibility to Nembutal than was found in cats, and in deep narcosis the EEG showed a different pattern from any found in cats.

10. The approximate correlation of EEG, by brain-wave count and by integrated electrical energy, and of the flexion reflex with Nembutal concentration in the blood is shown in table I.

11. A procedure for maintaining a desired level of narcosis, based on electrical-energy recording and independently-regulated Nembutal injection, is proposed in the final section of the Discussion.

We wish to acknowledge with gratitude the assistance of Mr. V. Sholund in the conduct of the experiments, of Mr. J. C. G. Loring and Miss Sarah Shaw in making brain-wave counts, and especially of Dr. Helen W. Deane, who did a major share of the work in preparing the paper for publication.

REFERENCES

ARAÑEZ, J. B. and FORTEZA, T. F. Kemithal sodium as general anesthetic for dogs. *J. Amer. vet. med. Ass.*, **1955**, *147*: 411-413.

BEECHER, H. K. and MCDONOUGH, F. K. Cortical action potentials during anesthesia. *J. Neurophysiol.*, **1939**, *2*: 289-307.

BEECHER, H. K. and MOYER, C. A. Mechanisms of respiratory failure under barbiturate anesthesia (Evipal, Pentothal). *J. clin. Invest.*, **1941**, *20*: 549-566.

BICKFORD, R. G. Automatic electroencephalographic control of general anesthesia. *EEG Clin. Neurophysiol.*, **1950**, *2*: 93-96.

BRODIE, B. B., BURNS, J. J., MARK, L. C., LIEF, P. A., BERNSTEIN, E. and PAPPER, E. M. The fate of pentobarbital in man and dog, and a method for its estimation. *J. Pharmacol.*, **1953**, *109*: 26-34.

CLOWES, G. H. A., Jr., KRETCHMER, H. E., MCBURNEY, R. W. and SIMEONE, F. A. The electroencephalogram in the evaluation of the effects of anesthetic agents and carbon dioxide accumulation during surgery. *Ann. Surg.*, **1953**, *138*: 558-569.

DEGELMAN, J. A coupling circuit for the Bickford integrator. *EEG Clin. Neurophysiol.*, **1956**a, *8*: 693-694.

DEGELMAN, J. A strain gage pneumotachograph. *EEG Clin. Neurophysiol.*, **1956**b, *8*: 517-520.

DERBYSHIRE, A. J., REMPEL, B., FORBES, A. and LAMBERT, E. F. The effect of anesthetics on action potential in the cerebral cortex of the cat. *Amer. J. Physiol.*, **1936**, *116*: 577-596.

DRIPPS, R. D. and SEVERINGHAUS, J. W. General anesthesia and respiration. *Physiol. Rev.*, **1955**, *35*: 741-777.

FORBES, A., BATTISTA, A. F., CHATFIELD, P. O. and GARCIA, J. P. Refractory phase in cerebral mechanisms. *EEG Clin. Neurophysiol.*, **1949**, *1*: 141-175.

FORBES, A. and MERLIS, J. K. The quantitative study of barbiturate narcosis. Rep. to Eastern Assn. Encephalographers, Dec. 1955.

FORBES, A., MERLIS, J. K. and BURLEIGH, S. Progress report on measurement of barbiturate narcosis. *EEG Clin. Neurophysiol.*, **1952**, *4*: 370.

FORBES, A., MERLIS, J. K., BURLEIGH, S., JIUSTO, J. H., MERLIS, G. L. and HENRIKSEN, G. Measurement of barbiturate narcosis. *EEG Clin. Neurophysiol.*, **1953**, *Suppl. 3*: 23.

FORBES, A., MERLIS, J. K., MERLIS, A. L. and BURLEIGH, S. Evaluation of barbiturate narcosis. *EEG Clin. Neurophysiol.*, **1951**, *3*: 380.

GAENSHIRT, H., KRENKEL, W. and ZYLKA, W. The electroencephalogram of the cat's brain at temperatures between 40°C. and 20°C. *EEG Clin. Neurophysiol.*, **1954**, *6*: 409-413.

KAHN, J. B., Jr. Studies in radioactive pentobarbital. *Cur. Res. Anesth. Analg.*, **1950**, *29*: 273-281.

KIERSEY, D. K., BICKFORD, R. G. and FAULCONER, A., Jr. Electro-encephalographic patterns produced by thiopental sodium during surgical operations: description and classification. *Brit. J. Anaesth.*, **1951**, *53*: 141-152.

KINOSHITA, J. H., BUNKER, J. P. and SCHOLANDER, P. F. The use of the volumetric respirometer in the determination of plasma carbon dioxide. *J. Lab. clin. Med.*, **1952**, *40*: 156-160.

PAPPER, E. M. and NGAI, S. H. Anaesthesiology. *New Engl. J. Med.*, **1954**, *250*: 1071-1078.

SINGER, R. B. and HASTINGS, A. B. An improved clinical method for the estimation of disturbance of the acid-base balance of human blood. *Medicine*, **1948**, *27*: 223-242.

SWANK, R. M. and FOLEY, J. M. Respiratory, electroencephalographic and blood gas changes in progressive barbiturate narcosis in dogs. *J. Pharmacol.*, **1948**, *92*: 381-396.

VERZEANO, M. Servo-motor integration of the electrical activity of the brain and its application to the automatic control of narcosis. *EEG Clin. Neurophysiol.*, **1951**, *3*: 25-30.

WALKER, J. T., FISHER, R. S. and MCHUGH, J. J. Quantitative estimation of barbiturates in blood by ultra-violet spectrophotometry. *Amer. J. clin. Path.*, **1948**, *18*: 451-461.

Reference: FORBES A., MERLIS, J. K., HENRIKSEN, G. F., BURLEIGH, S., JIUSTO, J. H. and MERLIS, G. L. Measurement of the depth of barbiturate narcosis. *EEG Clin. Neurophysiol.*, **1956**, *8*: 541-558.

THALAMIC CONTROL OF CERTAIN NORMAL AND ABNORMAL CORTICAL RHYTHMS

B. RALSTON, M.D. and C. AJMONE-MARSAN, M.D.
Department of Health, Education, and Welfare, U.S. Public Health Service, National Institutes of Health, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland

(Received for publication: May 7, 1956)

INTRODUCTION

The mechanism of production of certain types of electrical activity of the brain is still a controversial matter. The origin of many characteristic electrographic patterns which can be observed under different experimental conditions, as well as the origin of many physiological or pathological rhythms which can be recorded in the human EEG are still obscure. At the present stage of our knowledge, two facts seem to be well established; (1) elements of the cerebral cortex are capable of "spontaneous" electrical activity, and (2) afferent impulses from the periphery and from different subcortical centers are capable of modifying this activity and producing new types of electrographic patterns. Whether the cerebral cortex plays the role of a passive substrate in regard to this projected activity or whether it takes an active part ("secondary activation") and if so, to what extent, remains to be determined in each particular case.

The problem of determining the origin of various spontaneous rhythms is of obvious theoretical interest. The correct interpretation of a given pathological potential becomes, on the other hand, a matter of practical importance in the field of clinical EEG.

In the course of a series of experiments designed to study the electrographical behavior of artificially produced cortical and subcortical epileptogenic foci, we had the opportunity of making some interesting observations on the modifications of a well known and characteristic electrographic pattern, commonly referred to as "barbiturate spindles". In view of the fact that these rhythms have been identified by some authors with the alpha rhythm of man (3, 5, 6, 25); in view of the existence of some suggestive relationship between this activity and the responses elicitable from the non-specific thalamic system, and finally because of the well known, yet puzzling fact that sleep, and barbiturate sleep in particular, can activate certain types of epileptic discharges, it was felt worth while to investigate the phenomenon further.

The purpose of this study is to determine some of the factors involved in the mechanism of production of barbiturate spindles by analyzing the modifications which these undergo following subcortical lesions of a certain type. These lesions were made with penicillin, an agent possessing well known epileptogenic qualities (1, 31, 49, 50). As this agent, when injected into the thalamus, proved capable of producing a picture of sporadic paroxysmal high voltage bursts of slow and sharp waves either unilaterally or bilaterally synchronous, the question of relationship to certain pathological human rhythms and to the so-called "centrencephalic epilepsy" (46, pages 28 and 470) will be raised in the discussion of the findings.

MATERIALS AND METHODS

Adult cats were used in this study.

A total of 60 useful animals was studied; of these 16 animals had penicillin (aqueous-Squibb) (1×10^6 units/cc.) injected by micrometric control into various portions of the thalamus and in amounts ranging from .0025 cc. to .015 cc. Six animals had isotonic saline in similar amounts deposited at the same sites to act as controls.

In the remaining animals the drug was injected into various cortical loci, or (in a few) within the thalamus but in such an amount as not to allow precise localization and reliable interpretation.

The results from this last relatively large series of experiments, although not reported in the present paper, provide an extremely useful control for the study of electrical activity of the brain at various

TABLE I

RELATIVE INVOLVEMENT OF EACH MAJOR NUCLEAR COMPLEX OF THE THALAMUS IN DIFFERENT EXPERIMENTS. (B) STANDS FOR A BILATERAL LESION

Experiment	14	33	34	37	38	39	54	55	56	57	64	65	66	68	72	73
N. Reticularis	++															
N. Ventralis Ant.	++								+							
N. Ventralis Med.					+											
N. Centralis Med.			(B)			(B)				(B)				(B)		
Rhomboideus			+++	++	++	++				++				++		++
N. Reuniens			+		+++											
N. Centralis Lat																
Paracentralis		++	+	+			+	++	++						++	++
N. Supragenicul atus								++				+	+			
N. Centre Median					+		++	+++	++		++		+			
					(B)											
N. Medialis Dorsalis		+			+				+	+	+			+		+
Anterior Nuclei		+		+	+											
N. Ventralis Lat.	++						++									
N. Ventralis Post. Lat. and Med.							++	++	+++				++			
N. Lateralis Post.								+								
Pulvinar	+							+					+			
N. Geniculatus Med.												++	+			
N. Geniculatus Lat.																
Time (min.)	90	30	25	30	20	25	60	70	55	20	25	200	65	30	15	12
Dose (cc.)	.01	.0025	.0025	.0025	.01	.005	.0025	.01	.01	.005	.005	.0025	.0025	.0025	.0025	.0025

Dose is expressed in cc. of acqueous penicillin and refers to the minimal amount necessary to produce the various modifications of barbiturate spindles. Time is expressed in minutes and refers to the interval between the penicillin injection and the earliest appearance of these changes.

Note the main and almost constant involvement of nuclei belonging to the ''non-specific'' thalamic system. Note the longer delay for the EEG changes and the higher amount of penicillin needed to produce them when the ''center'' of the lesion lies within a nucleus of the ''specific'' (primary relay) nucleus.

levels of anesthesia under different experimental conditions, and in addition provide the necessary baseline to compare the subcortical and cortical effects of penicillin.

In two animals, the middle suprasylvian gyrus was undercut and insulated from subcortical regions and the effects of this procedure on spindle formation was studied.

All animals were tracheotomized and placed in a stereotaxic apparatus. Anesthesia was maintained by intravenous Pentothal, given in small increments just sufficient to produce active 8-12 c/sec. spindle bursts. Occasionally, supplemental curare and artificial respiration were employed. A few animals were initially anesthetized with ether and then maintained on curare and artificial respiration in order to study the effects of the thalamic lesion on the waking electrocorticogram.

No significant changes in the EEG pattern were observed during or following slow curarization, and, therefore, the presence or absence of curare in a given preparation will be ignored in the presentation of results or in their discussion.

A bilateral craniectomy was carried out, exposing both cerebral hemispheres to within 2 mm. of the midline, A right suboccipital craniectomy was made for introduction of the penicillin electrode. The exposed cortex was kept covered with warm mineral oil. The temperature of the animals was kept as constant as possible by means of a heating pad. Cortical recording was done through bipolar silver-ball electrodes with a 2-3 mm. interelectrode distance, mounted on the stereotaxic frame. Penicillin was introduced through a #22 spinal needle mounted on a stereotaxic carrier, introduced horizontally from behind. This needle was insulated down to the tip and was left in place at the site of the injection as a recording electrode. Thalamic recording was "monopolar" in order to obtain maximal information from the single deep electrode. The same indifferent electrode (lower eyelid or metallic frame of the stereotaxic instrument) was used for "monopolar" in cortical recording as well, for brief periods in each tracing. Placement of penicillin was determined by preliminary stimulation, utilizing the recruiting response for the non-specific thalamic system, and the short latency evoked responses of specific projection nuclei (such as ventralis lateralis postero-lateralis, ventralis postero-medialis, and medial geniculate) for guidance. An additional guide for all placements was the Jasper and Ajmone Marsan (27) stereotaxic atlas of the cat, and the terminology as well as the abbreviations for the subcortical nuclei employed are those used by these authors. The posterior subtentorial horizontal route, rather than the transcortical vertical, was utilized for injection in all but a few cases because:

(*a*) Even small amounts of penicillin tend to spread in a cylindrical shape parallel to the long axis of the needle, and for a distance of 2-3 mm. Injection from behind insured that the deposits would remain within certain fields such as the medial thalamic nuclei, the intralaminar, the ventro-basal, etc.

(*b*) Injection from behind also prevented back tracking into a transfixed lateral ventricle, when the electrode was introduced from above and the point lay in the subjacent thalamus.

(*c*) It was more convenient for the placement and rearrangement of cortical electrodes.

The penicillin and control saline injections were colored with cresyl violet to check on diffusion from the injected site. All placements were verified by frozen sections made of the whole brain at 50 microns and stained by the Nissl and Weil techniques. In addition, colored transparencies were made at the time of sectioning to evaluate the diffusion of the blue dye, as the particles could not be satisfactorily identified in stained sections.

Stimulation was by use of square waves (.2-.8 msec. in duration) generated by a Grass Model S4b stimulator.

Frequency of stimulation was 5-8/sec. for the recruiting response, and single pulses for the specific potentials. Optimal voltage was between 2-8 V. at the output of a 4:1 isolation transformer (GR 578-A). Recording was carried out with an 8 channel type D3 Offner Electroencephalograph with provision made for monitoring 2 channels at a time through a Dual Beam Type 322-A Dumont cathode-ray oscillograph. The time constant was generally kept at .1 sec., a value which proved satisfactory for recording of the spindle activity. However, various portions of the record were also taken with the maximal available time constant (.35 sec.).

Continuous recording at different speeds was made for a minimum of 5 hours and usually from 7-10 hours. Cortical electrodes were left in place during the major part of an experiment in order to better evaluate changes at a given point, and at the end, were rearranged for a more complete cortical survey. The gain of the amplifiers was usually set so as to get approximately 1.5 cm. pen deflection for an input of 250 μV. No absolute values of amplitude are given in the presentation of results or in the samples selected for illustration. It is our feeling that the relative differences in amplitude between paroxysmal transients and the background activity in the same channel or between two different channels are far more significant and convincing than the absolute values (which, in addition, can be affected by many non-biological factors). In any case, in all the following illustrations, the gain is kept constant throughout the same experiment.

At the termination of the experiment, both

carotids were intubated with polyethylene catheters, the animal sacrificed with an overdose of Pentothal and the brain perfused, first with normal saline and then with 10 per cent formalin in an overnight drip. On the following day the plane of section of the hardened brain was determined in the stereotaxic apparatus before removing it from the skull. This duplicated the frontal plane of the atlas and facilitated identification of structures.

RESULTS

The results of injection of aqueous penicillin into the thalamus of the cat were an almost invariable alteration of the 8-12 c/sec. spindle activity present over various cortical areas, following intravenous Pentothal. This was true irrespective of the location of the penicillin within the dorsal thalamus, although as will later be shown, the distribution of the changes varied considerably, depending on the site of the lesion. The alteration was unrelated to the amount of penicillin, being just as pronounced with the smallest injection (.0025 cc.) as with the largest (.015 cc.). When the larger amounts were given (in increments of .0025 cc. every 15 min.), a spiking focus was finally produced but the spindling alterations antedated this, and were in no way dependent on its presence or absence. The alterations of the spindles were of two major types:

(1) Slowing from 8-12 c/sec. to 3½-5 c/sec.

(2) Synchronization of spindle bursts.

In 75 per cent of the cases, both were present, while in 15 per cent only slowing was encountered and in 10 per cent only synchronization. It is possible that with more extensive cortical recording, a greater congruence would be present.

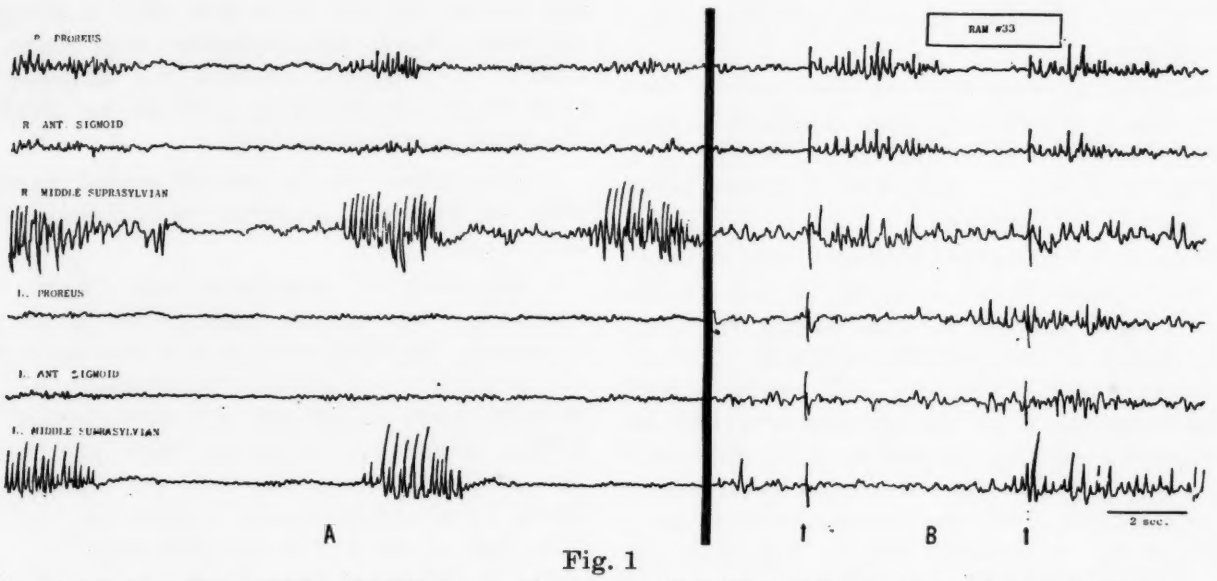


Fig. 1

A. Normal control record showing a tendency to transient spindle "synchronization".

B. Response to single shock stimulus of right nucleus centralis lateralis.
The stimuli are indicated by arrows. The first stimulus triggers spindle formations in the right 3 leads only. Just prior to the second stimulus, spontaneous discharges have begun in the left cortical leads. These are unaffected by the second stimulus whereas spindles are again induced on the right side.
The distribution of the "triggered" spindles is identical to the cortical areas from which abnormal discharges are obtained following penicillin.

Before discussing these changes in detail, it may be of value to see how they might apply to a typical experiment.

RAM # 33. Preliminary cortical recording was carried out which showed asynchronous spindling in all leads. The penicillin electrode was first used for electrical stimulation. It was introduced on the right from behind and slowly advanced until a recruiting response was obtained (parameters of stimulation: 6 V., 6 c/sec., pulse duration .2 msec.). This was

predominately in the right proreus and the right anterior sigmoid gyri. Single stimuli resulted in the triggering of 8-12 c/sec. spindles in these same areas and in the right middle suprasylvian region (fig. 1). Subsequent histological examination showed the electrode tip to be in right n. centralis lateralis about 2 mm. from the midline. The lesion produced in the same area by the injection of .0025 cc. of aqueous penicillin (1 x 10^6 units/cc.) colored blue with cresyl violet is seen from the prints made from colored transparencies, taken as frozen sections were being made (fig. 2). This appears as a small dark area located in the right thalamus, about 2 mm. from the midline and extending over 4 mm. antero-posteriorly. Figure 3 shows the same lesion as reconstructed from the microscopic sections. It is seen to extend through nuclei anteromedialis, centralis lateralis and medialis dorsalis. There is no involvement of the nuclei of the midline or of the primary sensory relay nuclei. Most of the lesion lies within those nuclei designated as the non-specific thalamic system, and from which a recruiting response may be obtained. A part of the medialis dorsalis is also included in this system.

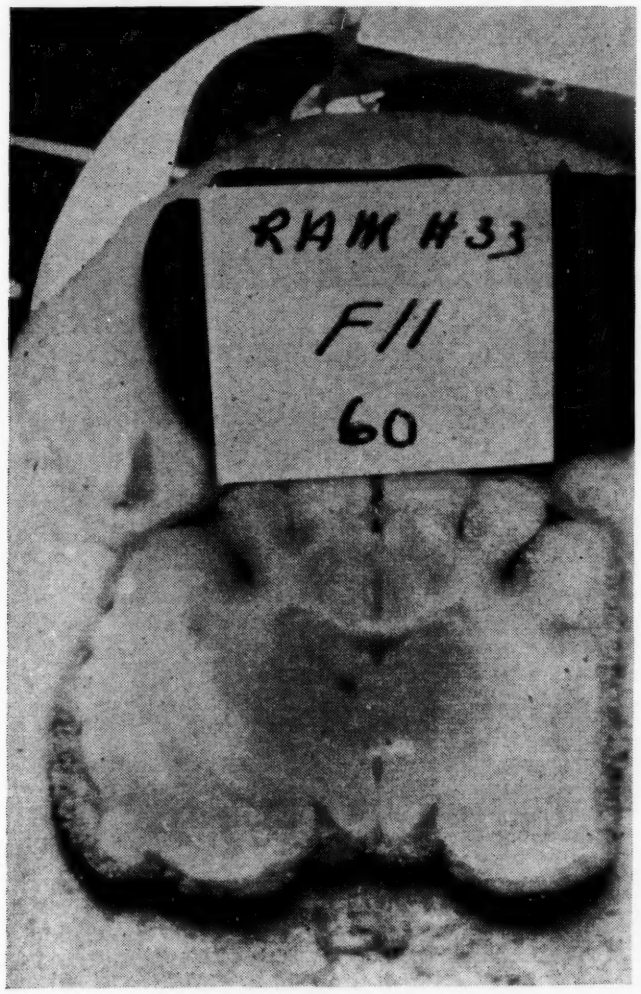


Fig. 2

Photographs were taken during the preparation of frozen sections of the whole brain for microscopic study. The extent of the penicillin lesion is indicated by the dark color which is due to the addition of cresyl violet prior to injection. This method was routinely employed as an additional check on the diffusion of the penicillin. It indicates the relative discreteness that may be obtained with small amounts of penicillin (.0025 cc.). The F number on the card indicates distance in mm. in front of the interaural plane.

Following the injection of penicillin, continuous recordings were made both from the cortex and from the thalamic site of injection (n. centralis lateralis) (fig. 4). Within 25 min. the spindles of the right proreus, anterior sigmoid and middle suprasylvian gyri had become synchronized and their frequency slowed to about 8 c/sec. These changes were not present in the right posterior suprasylvian area nor in any of the left sided leads. Ten minutes later, the slowing had progressed to 5-6 c/sec. The spindle had "spread out", being about 1½ times in length and had increased about ⅓ in voltage. Within 45 min. the frequency of the right sided anterior leads had dropped to 4-5 c/sec. and they had become relatively synchronous with bursts of slow waves of 3 c/sec. in the thalamus. Within one hour after the injection, spike components were seen within the altered spindle bursts only, appearing on the rising phase of the wave and bearing a suggestive resemblance to the 3/sec. "wave and spike" complex. At this time, recording from ipsilateral middle ectosylvian, middle lateralis and posterior suprasylvian disclosed bursts synchronous with the anterior and thalamic leads. When the spikes were large and occurred at the beginning of the altered spindle, they tended to synchronize the activity even more sharply. It is of interest to note that the anterior leads (proreus and anterior sigmoid), tended to discharge first, this being reminiscent of the results obtained by single shock stimuli to the same region of the thalamus (25). Following this, a Metrazol activation was carried out and the electrographic seizure thus elicited showed its onset in the thalamus.

This case illustrates the gradual evolution from the normal 8-12 c/sec. spindle activity to the 4-5 c/sec. bursts. In this case it is associated with increased voltage and prolongation of the spindle. It also shows progressive synchrony, beginning anteriorly and spreading posteriorly on the right, all of these phenomena taking place in association with a right sided thalamic lesion. In this case there is later intermittent spiking, occurring during the burst activity and creating a "wave and spike" appearance in the thalamus. This delayed spiking and the specific Metrazol activation suggest the "epileptogenicity" of the penicillin lesion.

The early distribution of the discharges is also similar to that of the recruiting responses and of the response to single shocks which were obtained from the same thalamic region prior to the injection of penicillin.

With this illustrative case before us, the various individual phenomena can be further examined with reference to the series as a whole.

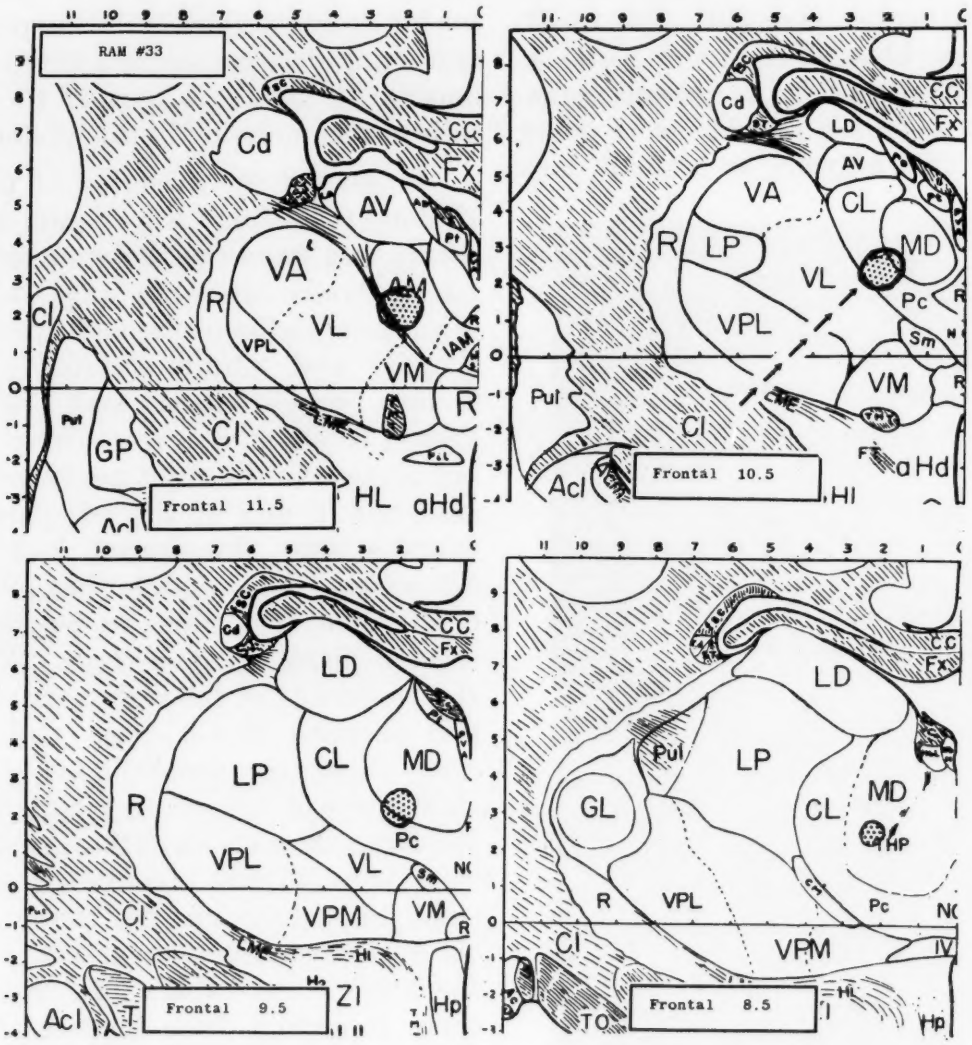


Fig. 3

Reconstruction of the penicillin lesion from Nissl and Weil stains. The arrows indicate the position of the recording (and stimulating) electrode. The lesion is seen to involve antero-medialis, centralis lateralis, and part of medialis dorsalis nuclei of the thalamus.

1. Modifications of the Spindle

Intrinsic frequency. Slowing of the intrinsic frequency of the spindle occurred in all the animals but one. The slowing would take place progressively and would often reach the

value of 3-5 c/sec. (fig. 5). One animal showed only a drop from 12 to 8 c/sec. This would not ordinarily be considered of significance, but since it occurred ipsilaterally to the lesion where it was present in all the leads and was associated with a widespread hemispheral synchronization, it might be included among the positive results.

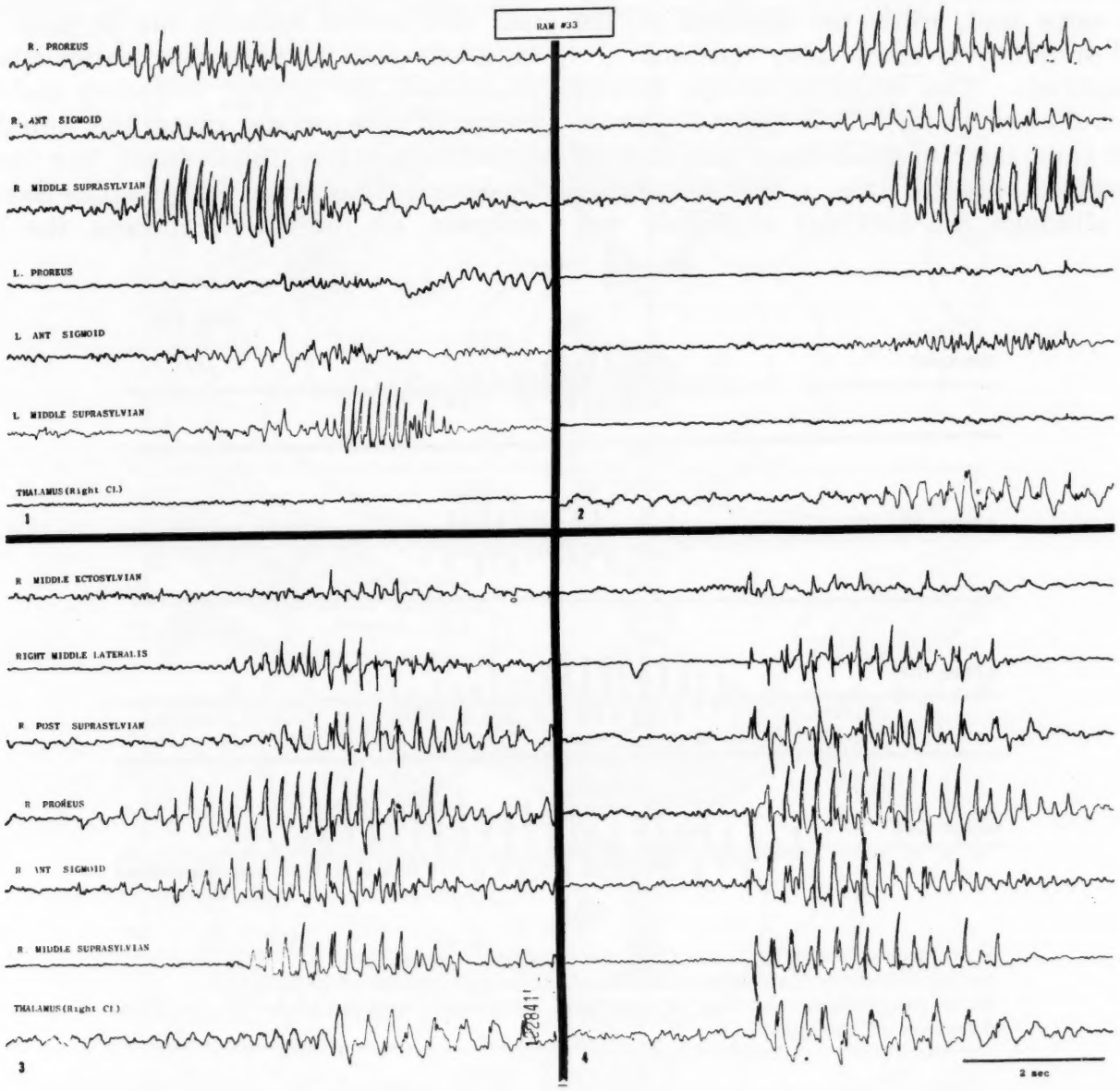


Fig. 4

(1) 25 min. following the injection of penicillin in right CL (see fig. 2 and 3).
See control in figure 1.
The right sided spindles have increased in voltage and slowed to about 8 c/sec. Although there was a very occasional tendency of the right sided leads anteriorly to synchronize before penicillin, a permanent synchrony is now established. A normal left sided spindle is present.

(2) 45 min. following injection of penicillin.
The frequency of the right sided spindles has decreased to 4-5 c/sec. Left sided spindle frequency is unchanged. There are now synchronous slow waves in the thalamus.

(3) 60 min. following injection of penicillin.
(Note that all leads are now from the right side and the order is changed). There is high voltage slow activity appearing in bursts from the whole hemisphere, appearing first in anterior regions. Sharp waves are now occasionally superimposed upon the burst.

(4) A few minutes after 3.
This record again shows the presence of widespread synchronous bursts appearing from a relatively normal background. More spiking is evident and in the thalamus particularly, a pattern suggestive of "spike and wave" has been established.

Duration. Generally, the length of the altered spindle was prolonged to almost twice that of its original form (fig. 5) and of the control (non-involved) spindles. The length of a normal spindle tended to vary somewhat in the same lead, while the duration of the altered spindle was much more constant.

Amplitude. The majority of the slowed spindles showed an amplitude about 1½ times greater than their original form and that of non-involved spindles (fig. 1 and 4). Sometimes, although the maximal amplitude was no greater than that of the ''peak'' of the normal spindle, a much larger number of the waves of the altered spindle, would reach this value (fig. 7). In a certain number of cases, however, no significant increase of voltage was noted.

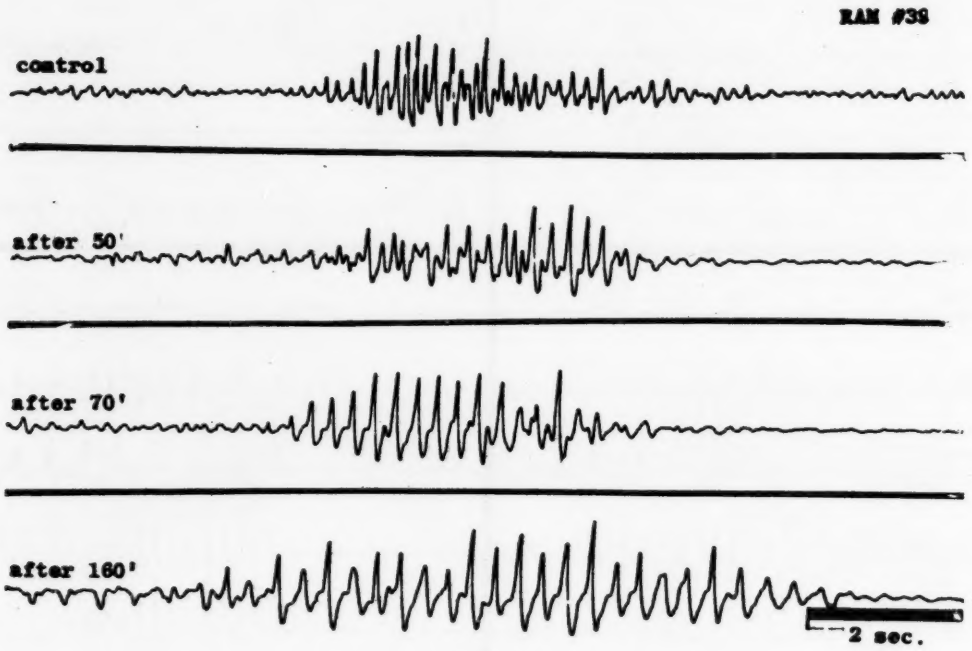


Fig. 5
Example of modifications from a ''normal'' spindle to a ''deteriorated'' one at different time intervals after thalamic injection of penicillin.
Note progressive slowing of intrinsic frequency and increase in the total duration of the spindle.

Shape. The shape of the normal spindle is characterized by a series of irregular waves, some large and ''spike-like'' and others smaller and sometimes more rapid. These tend to intermingle. On the contrary, the altered spindle approaches a sinusoidal form which rises to a peak and falls uniformly, the individual waves averaging from 200-330 msec. in duration (this is in contrast to the general effect observed with high doses of barbiturates where the deteriorated spindle is composed of sharp waves separated by a flat base line). The difference between abnormal and normal spindles can be most advantageously seen at very slow paper speed. In the normal, the greater frequency and irregularity of the waves gives the spindle the appearance of a thick fused bar near the isoelectric line from which spike-like waves emanate at intervals, whereas the altered spindle has no such ''bar'' and can be ''seen through'' at all points (fig. 7, 11).

Frequency of repetition. The number of spindles per minute is usually decreased in those leads which show altered spindles (fig. 7-11).

Background activity. The interspindle activity frequently shows an irregularly rhythmical slowing down to 3 c/sec. waves of low amplitude which tends to be more prominent in the vicinity of the spindles and seems to be independent of the amount of penicillin used in producing the lesion (fig. 5, 7, 11).

Relation to recruiting response. Generally,

the localization of slow spindling would correspond to that of the recruiting responses or of the triggering of single spindles by single shocks stimulation (fig. 1, 4). If these were bilateral, the effect would be bilateral, and if unilateral, the effect would be unilateral.

the usual 8-12 c/sec. activity but spindles at the new frequency (fig. 14). If, in addition to slowing, spike activity was present in the thalamus following penicillin injection, it, too, could "trigger" (and synchronize) the altered spindles (fig. 13-15).

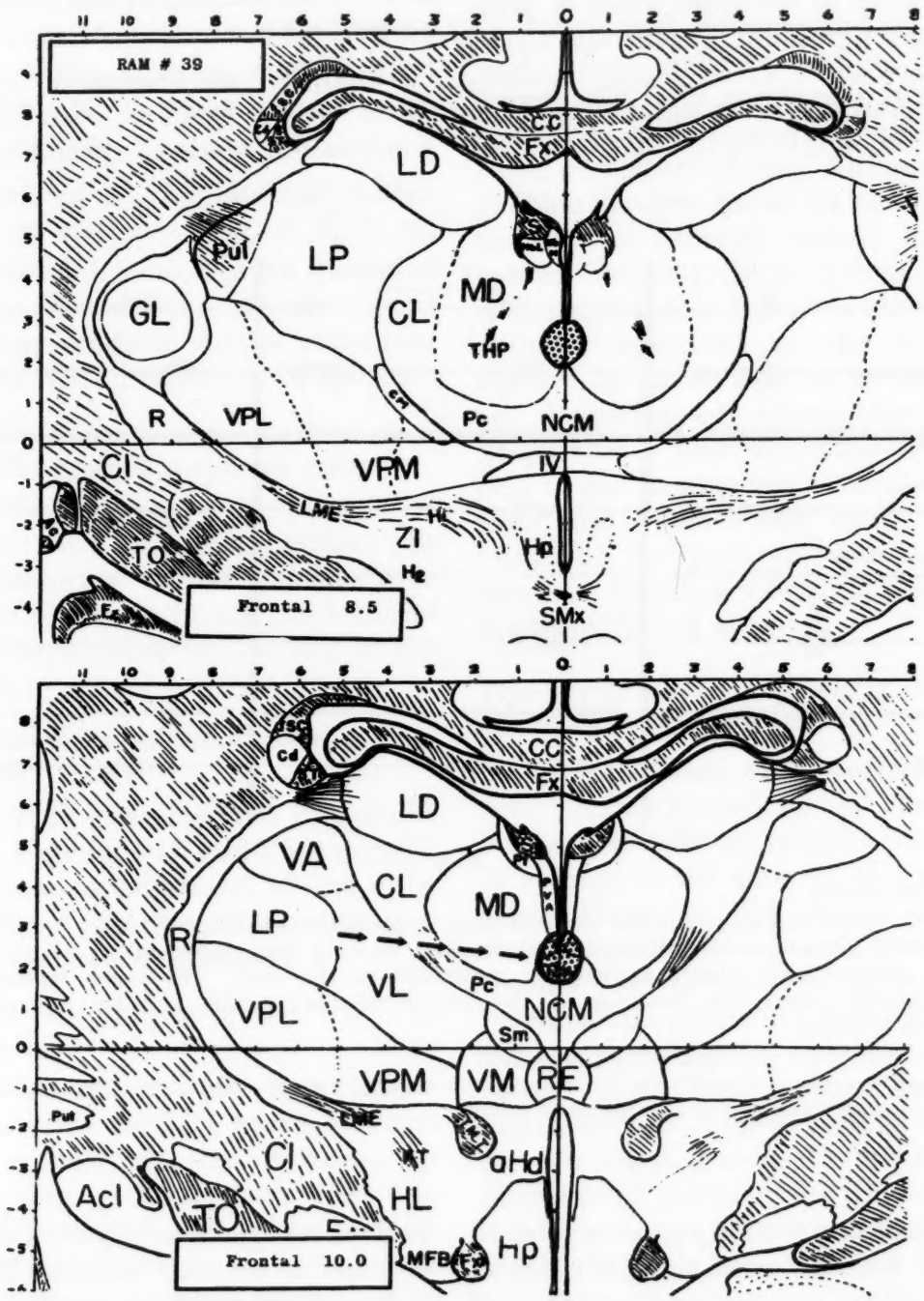


Fig. 6

Outline of the penicillin lesion based on microscopic sections. The arrows indicate the site of the recording electrode.

The anteroposterior distribution in the hemisphere also coincided. In cases in which single shock stimulation with spindle triggering was tested both before and after the establishment of slowed spindles, the latter would evoke not

2. Synchronization

By synchrony is not necessarily meant a one to one temporal relationship of each of the waves within the different spindles (although this can occur), but the simultaneous appear-

ance and constant co-existence of the spindles over two or more areas of one or both hemispheres. As defined, the presence of synchrony was sought for in all of the 60 electrocorticograms in which the conditions of anesthesia were as described (Materials and Methods) and prior to the application of penicillin. Although persistent synchrony might be observed between 2 areas closely related, as the anterior and posterior sigmoid gyri for instance (and this might be biological or simply due to electrode proximity), no persistent synchrony was seen between the activities of the anterior, middle and posterior portions of one hemisphere. This was equally true in comparing side to side. For brief periods large areas would appear to be synchronous but this was very transitory. From this it was felt that the observation of a persistent unilateral or bilateral synchrony was of significance with reference to the lesions produced. Persistent synchrony was present in 85 per cent of the animals with penicillin lesions. The topography of the cortical synchronization depends on the location of the thalamic lesion and will be discussed in the next section.

The Relationship of the Spindling Alterations and Synchronization to the Location of the Lesion

Because, as illustrated above, the penicillin never remains restricted to a single nucleus but tends to spread anteroposteriorly and to diffuse laterally to a certain extent, it is more in keeping with the facts to speak in terms of subdivisions in areas rather than in nuclei, and to indicate by representative illustrations the various nuclei that are involved to a varying degree in each region.[1] Towards this end, the following divisions have been made.

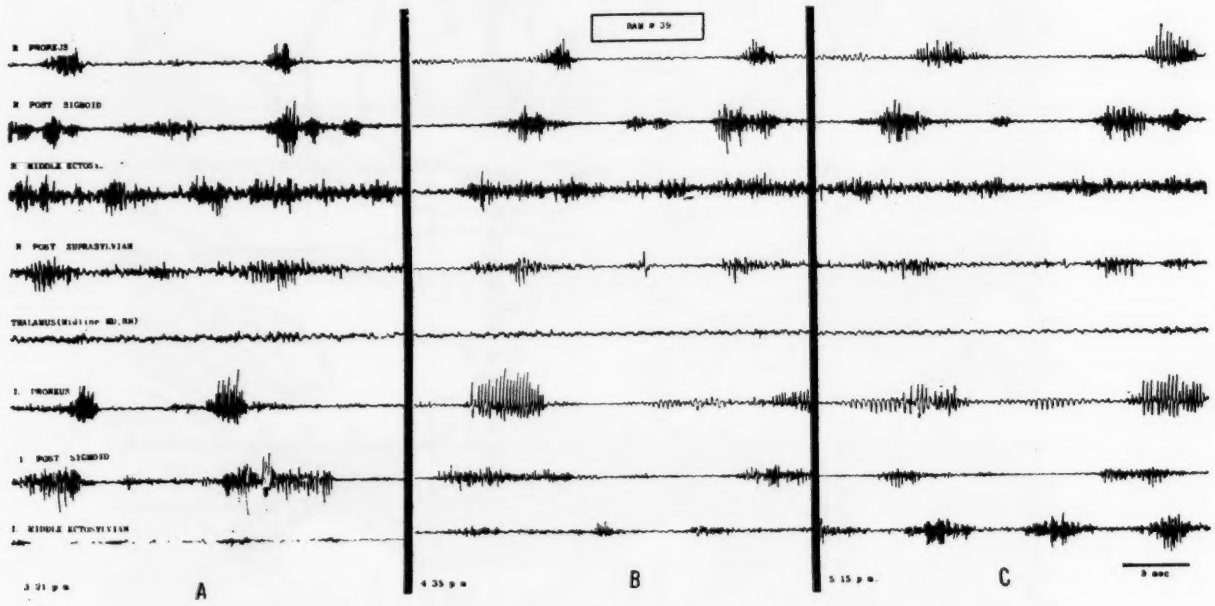


Fig. 7

A. Control record.

B. Record 1 hour and 15 min. after the injection of penicillin (see fig. 6).
The record remains asynchronous but marked slowing has developed in the left proreus lead, giving the ''clear'' appearance described in the text. The more regular form of the spindle waves, the increase of the length of the spindle and its generally higher voltage is noted.

C. Record 2 h. after the injection of penicillin.
The same process starts now to involve the right proreus. Note also the regular slowing of the background in the two involved leads.

[1] For the relative involvement of each thalamic nucleus in different experiments, see table I.

(*a*) *Lesion in the massa intermedia* (fig. 6-7).

Minimal midline lesion produced slowing of the spindles of both prorei only without synchronization.

(*b*) *Lesion just lateral to the midline but impinging on it* (fig. 8-9).

All records were characterized by slowing and synchrony in the anterior regions, first ipsilateral to the site of penicillin injection and, later on, bilateral.

(*c*) *Lesion restricted to the internal medullary lamina of one side* (fig. 1, 2, 3, 4).

The effects of such lesions were discussed in detail in the description of experiment RAM # 33. Large midline lesions extending 2.5 mm. from the midline resulted in synchrony in all leads.

(*d*) *Lesion in the specific primary relay nuclei* (fig. 10-11).

The records were all characterized by slowing and synchrony of the spindles over the anterior two-thirds or in all the leads of the hemisphere homolateral to the site of the penicillin lesion.

(*e*) *Lesion in the dorsolateral thalamus* (fig. 12-13).

The records were characterized by spindle slowing in the homolateral middle suprasylvian gyrus with no involvement of the anterior regions where spindles of normal configuration and frequency persisted.

Comment on the topography of the spindling alteration.

These findings seem to indicate a pattern whereby the anterior cortical areas are represented most mesially in the thalamus. A midline lesion may activate each side separately or synchronously. A lesion just eccentric to the midline involves its homologous cortex first and then, possibly as the lesion enlarges, may involve the other side. Further laterally, an entirely ipsilateral effect is obtained which may involve the whole hemisphere. This seems to be true of lesions still further laterally with maximal involvement of the specific afferent systems but which do, however, infringe on their periphery in the non-specific system (nuclei supragenicularis and centralis lateralis). A lesion further dorsolateral in the thalamus no longer involves frontal cortical regions.

The Effect of Thalamic Penicillin Lesions on the Electrocorticogram of the Non-Anesthetized Animal

In several animals initially anesthetized with ether and thereafter maintained on curare and local anesthesia, penicillin was introduced into thalamic regions similar to those described above. Although the electrographic pattern prior to this procedure was that of an aroused animal and showed no spindle activity, large bursts of slow waves indistinguishable from the altered barbiturate spindles appeared in the ipsilateral hemisphere 30 to 60 min. after injection. Later on, Pentothal was administered in the same preparation. This would induce normal spindling in the hemisphere contralateral to the lesion and enhance the slow "deteriorated" bursts on the ipsilateral side: no normal barbiturate spindles would appear in the ipsilateral affected areas.

The Effect of Local Cortical Undercutting on the Barbiturate Spindles

Undercutting of a cortical area, which prior to this procedure had shown active barbiturate spindling, resulted in a general fall in voltage in the activity of partially isolated area. However, the action was disproportionate in that the rapid, low voltage interspindle activity persisted only slightly altered in shape and frequency while the much higher voltage barbiturate spindles totally disappeared. Additional increments of barbiturate enhanced spindling generally but did not affect the isolated area. Following the local application of acetylcholine in this same region, a small amount of low voltage rhythmical activity could be induced, but this effect was rather transitory.

Controls

A few experiments were divised in order to determine whether the above-described effects upon spindling activity were dependent upon a specific type of thalamic injury, and therefore directly related to the penicillin (even though in sub-convulsive doses), or

whether the effects were the result of a purely mechanical, destructive lesion of the thalamus.

Injection of similar amounts of isotonic saline into various mesial and lateral thalamic areas under the usual experimental conditions constantly failed to induce any significant

DISCUSSION

From the data presented, it has been shown that the introduction of small quantities of penicillin into the thalamus results in alteration of the 8-12 c/sec. barbiturate spindle, with or without spiking activity and with a tendency toward synchronization. The

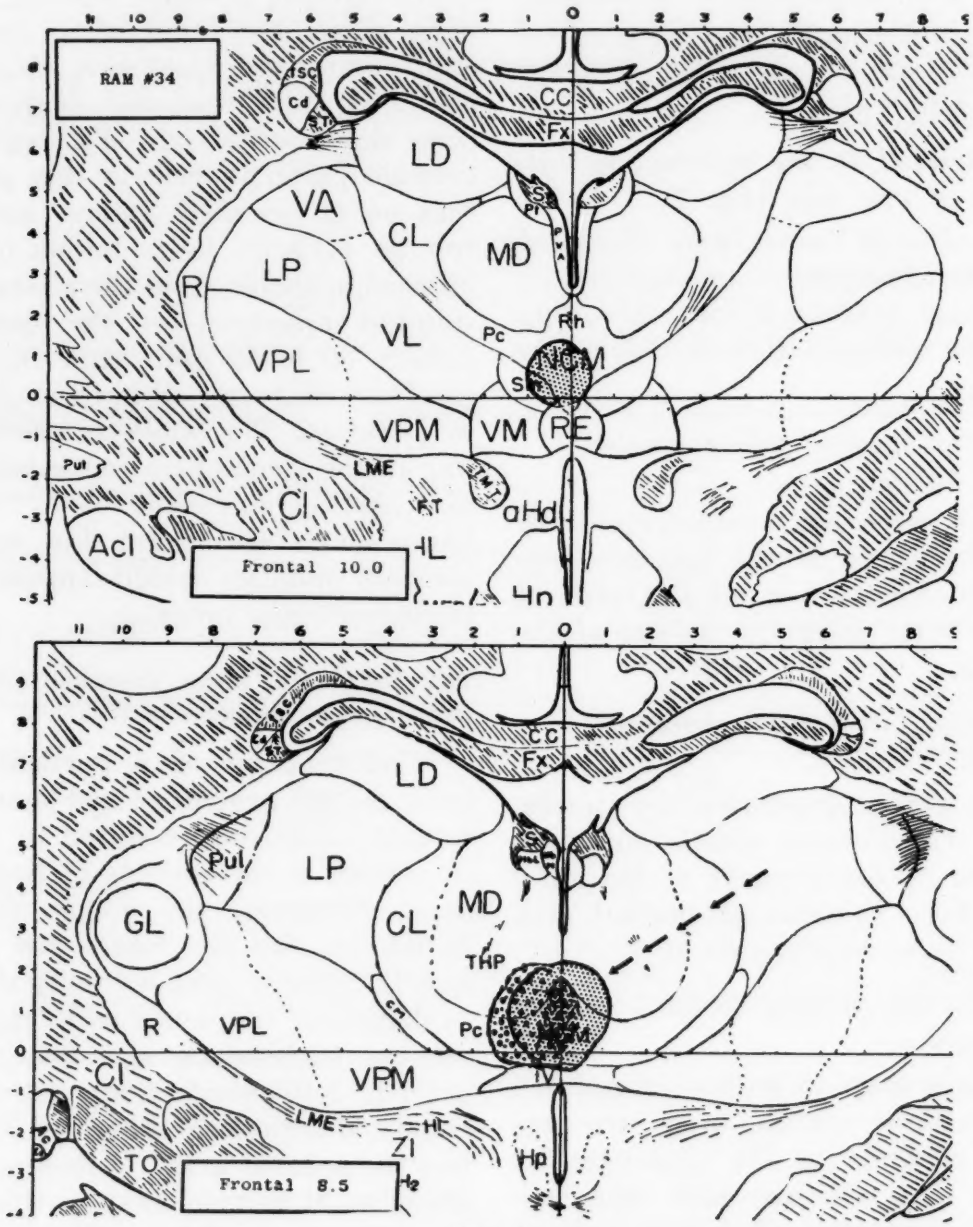


Fig. 8

Position of the lesion based on microscopic sections. The arrow indicates the site of the recording electrode. The penicillin lies slightly more to the right of the midline in the more anterior sections.

change in the organization, frequency, morphology or amplitude of the pre-existing spindle activity. Only occasionally, towards the end of a long experiment one could observe a diffuse generalized slowing of moderate degree of the intrinsic frequency of the spindles.

cortical topographic distribution of these changes has been shown to be related, to a certain extent, to the location of the thalamic injection and the resulting "lesion". The interpretation and significance of these changes will be discussed from the following points of view.

1. *Origin of the "barbiturate spindle".*

From a survey of the literature on the subject, it would appear that there are at least two basically different viewpoints concerning the genesis of the 8-12 c/sec. cortical activity.

One school of thought, represented primarily by Bremer (3, 5), maintains that these cortical rhythms are "autonomous", and that the main function of the thalamus is to provide a non-specific "tonus cortical", which would create the dynamogenic conditions ne-

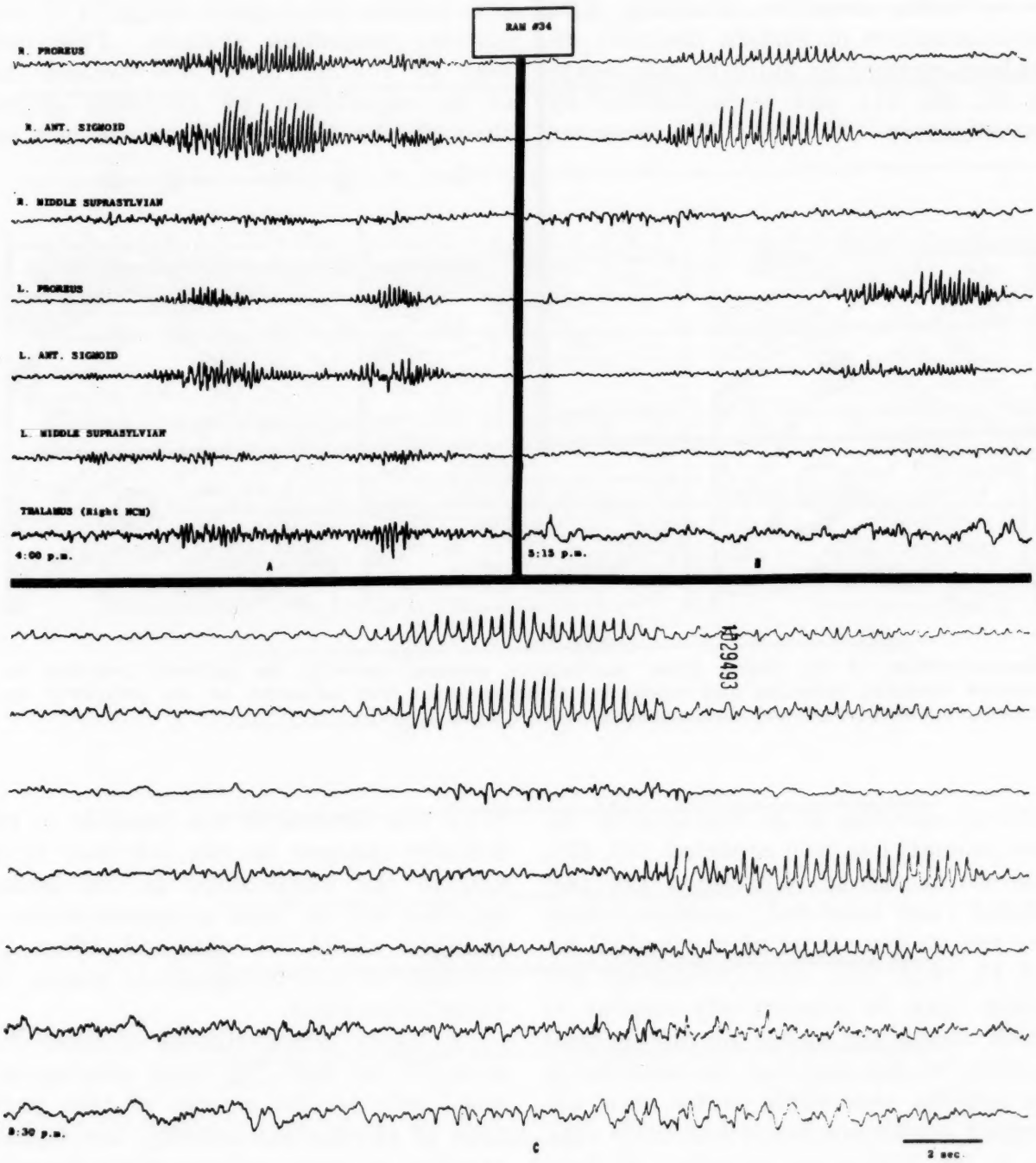


Fig. 9

A. Record made 20 min. after the injection of penicillin (see fig. 8).
There is an independent synchrony over the anterior portions of both cerebral hemispheres with spindling of normal frequency.

B. Record 1 h. after penicillin.
Considerable slowing in both anterior right sided leads.

C. Record 4 h. and 15 min. after,penicillin.
Slowing of the spindles has continued on the right side and now involves the left anterior regions. The synchrony is unchanged.

cessary for this autonomy to express itself. These conclusions are drawn mainly from studies with isolated cortex (2).

The second school places the origin of these rhythms within the thalamus or other related basal structures. The great similarity between the spontaneous barbiturate spindles and the recruiting response, elicitable with electrical stimulation of certain thalamic regions has been stressed by Morison and Dempsey (10, 11, 40, 41) and re-emphasized by other investigators (25, 26). The presence spontaneous rhythms present in the cortex and, particularly, in a slab of cortex isolated from other cortical and subcortical influences.

The present method of introducing small quantities of penicillin into more or less discrete portions of the thalamus, permits a study of the spindle activity in an intact preparation with relative integrity of thalamocortical projection systems. This integrity may be further confirmed toward the end of an experiment by electrical stimulation through the thalamic electrode left *in situ*.

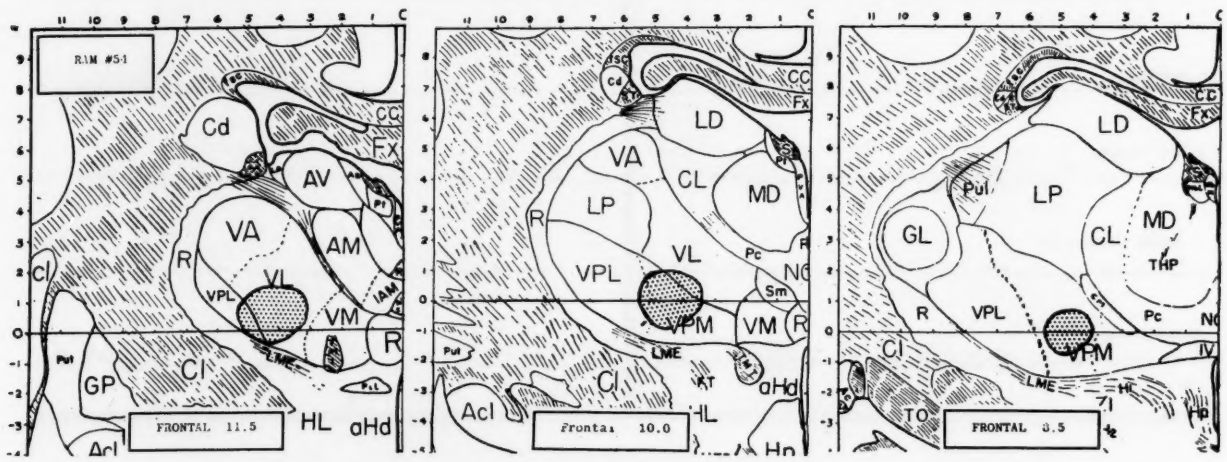


Fig. 10

Reconstruction of the lesion from microscopic sections showing its primary position in nucleus ventralis lateralis and ventralis posteromedialis but adjacent at its periphery to reticularis and (not shown) centre median and centralis lateralis.

of barbiturate spindles in the thalamus of decorticated animals has been reported (39, 42).

While we accept as established the fact that isolated (and insulated) cerebral cortex may give rise to some type of rhythmical activity (2, 13, 14 20, 35), whose frequency and morphology may be suggestively similar to that which forms the object of our present investigation, we also feel that the attenuated, sporadic activity observable under such unphysiological conditions bears but little relationship to the 8-12 c/sec. spindle. Without being willing to diminish the significance of Bremer's theory on the genesis of the "spontaneous" intrinsic activity of the cortex, we hesitate (at least until more convincing evidence is provided), to indentify the characteristic, well defined spindle activity appearing during barbiturate sleep, with the With this method it was possible to produce definite changes in the intrinsic frequency and in the morphology of the barbiturate spindles and in their synchronization: these changes would be obtained after passing through various intermediate stages, as previously described.

A likely interpretation of these findings seems to be that, far from playing a "passive" role in the genesis of this particular type of rhythmical activity, the thalamus is capable, at least under certain experimental conditions, of markedly modifying it in regard to shape, frequency, voltage and organization. Thus the hypothesis is confirmed that the chief anatomical substrate for the mechanism of the barbiturate spindles is likely to be located in subcortical structures, possibly in the thalamus (7, 37, 39, 42). From

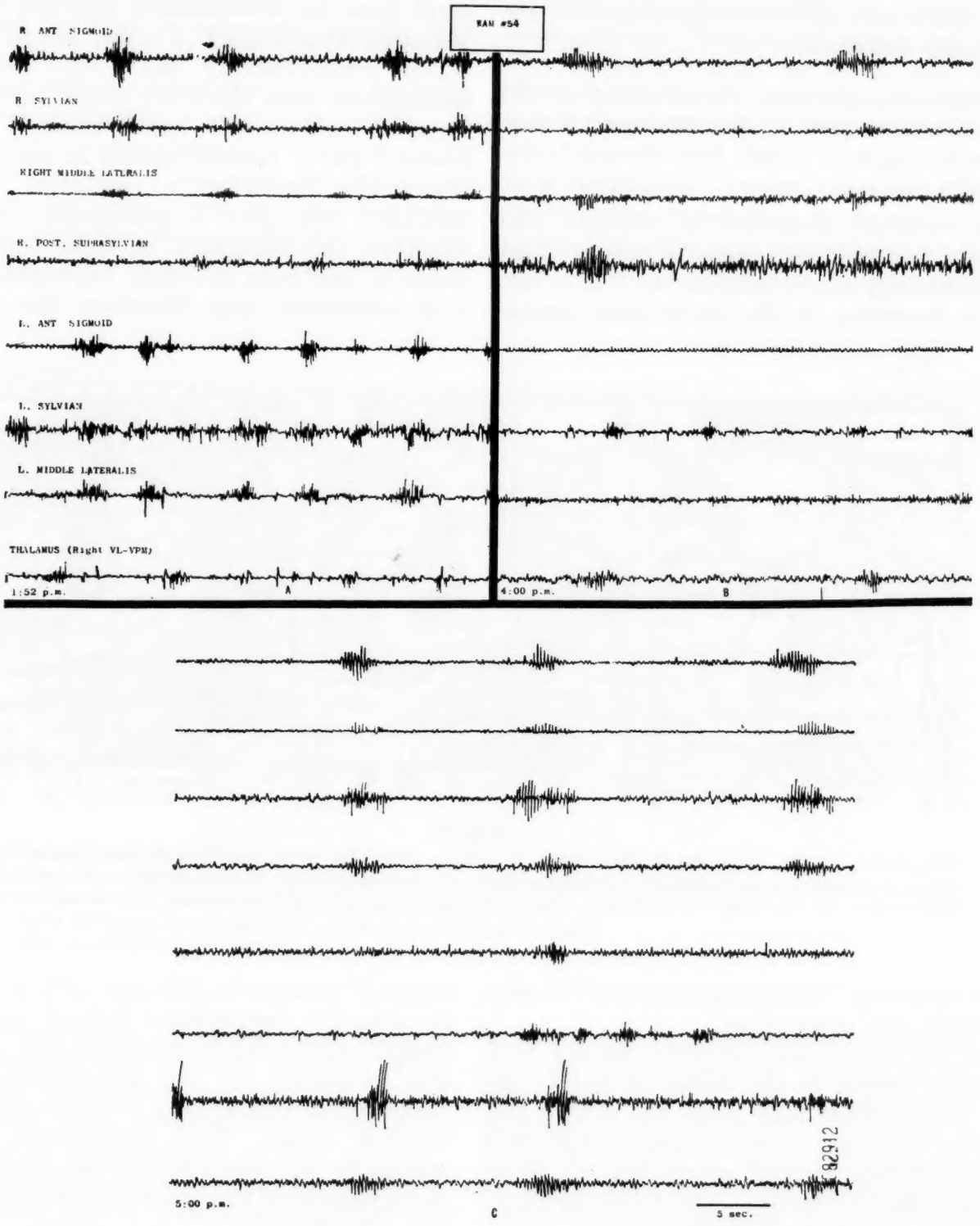


Fig. 11

A. Control record.
This record shows asynchronous spindling of normal frequency in all leads.

B. Record 1 h. after injection of penicillin (see fig. 10).
There is slowing and synchronization of all leads on the right side and in the thalamus. Asynchronous spindling still persists on the left.

C. Record 2 h. after penicillin.
Further slowing in all right sided leads and the thalamus. Note the greater length of the spindles, the greater uniformity of their waves and the regular slowing of the background in channel 1, in the vicinity of the altered spindle.

there, they are "projected" to the cerebral cortex whose neurons would therefore be only secondarily activated.

2. *Relationship between the changes of the barbiturate spindle, the thalamic "non-specific system" and the "arousal system".*

The evidence presented by Morison and Dempsey, and later by others, to indicate that a strict analogy exists between the 8-12 c/sec. activity occurring in the barbiturate preparation and their "recruiting response" is very suggestive and convincing.

As the 3.5-5 c/sec. spindles elicited with penicillin lesions in the thalamus clearly appear to be derivations from the 8-12 c/sec. activity, it is reasonable to assume that their thalamo-cortical spread occurs via the thalamic non-specific system. The following findings tend to confirm this impression:

(*a*) the spindle slowing tends to develop in those leads in which a single shock stimulus triggers the 8-12 c/sec. activity;

(*b*) the distribution of the spindle slowing and synchronization falls into a pattern which has been described in the preceding section of Results.

Briefly, midline lesions tend to affect both anterior hemispheric regions. Slightly eccentrically placed lesions affect first the ipsilateral then the contralateral anterior regions (bilateral synchrony). Further lateral lesions affect predominantly the whole ipsilateral hemisphere (and therefore larger midline lesions will affect both hemispheres in a generalized way). Lesions placed in primary relay nuclei (such as n. ventralis posterolateralis) also give a generalized response, however, the periphery of these lesions include n. centralis lateralis, suprageniculatus and reticularis and therefore the delayed

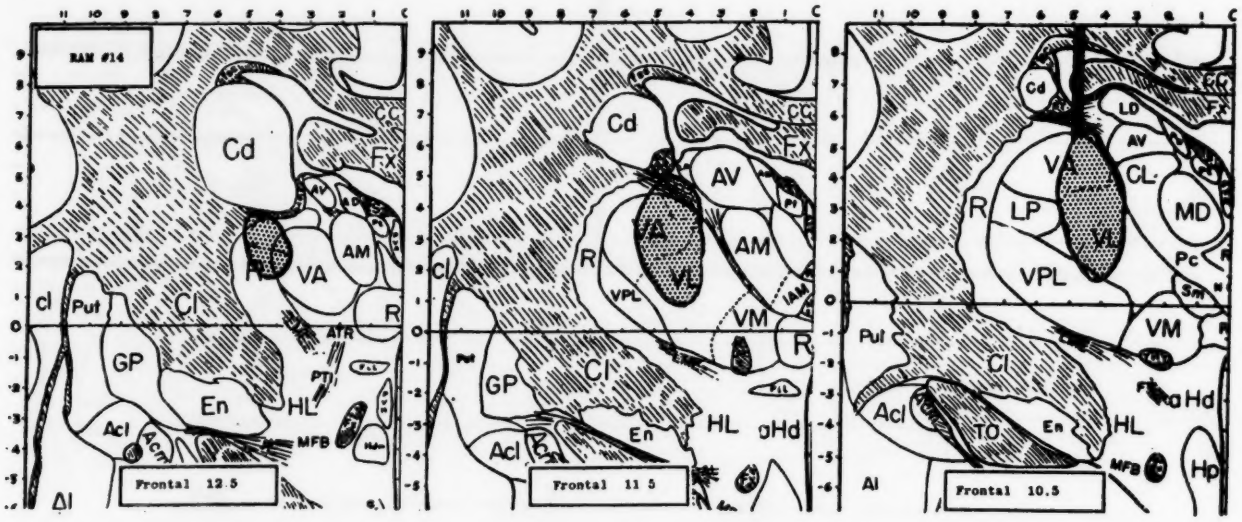


Fig. 12

This lesion is the only one in the series in which penicillin was introduced from above (in order to reach the dorsolateral thalamus which is inaccessible by the posterior route without destruction of the bony tentorium). The dark line indicates the placement of the electrode.

onset of changes in this case (90 min. versus 30 min. for paramidline lesions) suggests a probable diffusion of penicillin into these nuclei belonging to the non-specific system. Dorsolateral lesions tend to spare the cortical anterior areas. This distribution is very similar to that described for the topographical arrangement of the thalamic non-specific system (18, 25, 29);

(*c*) whereas single shock stimuli in the thalamus tend to trigger normal spindles at the onset of an experiment, stimulation at the same point after penicillin-induced slowing of the spindles will trigger the new slowed responses (fig. 14);

(*d*) the synchronization which develops as a result of the penicillin effect, includes predominantly the slowed spindles and cor-

responds to the synchronous spindle triggering produced by single shocks.

These findings in aggregate suggest that the synchronization effects as well as the slowing of the spindles occur through the thalamic non-specific system.

Magoun and associates (38, 44) have shown that stimulation of an area in the upper mesencephalic tegmentum or basal diencephalon will abolish barbiturate spindles; destruction of this area in a waking animal will, on the contrary, induce a rhythmical activity of a type very similar to these spindles while large lesions of the thalamus will again abolish the spindles. They interpret these findings as indication of the existence of an ''arousal'' system, extending up in the upper midbrain, which, when active, can de-synchronize the cortical activity therefore interfering with the spindle formation, while, when inhibited or destroyed, will permit spindling to occur in certain regions of thalamus and cortex. Evidence for a subcortical, extrathalamic origin of the barbiturate spindles (45) has not been confirmed.

Although such massive lesions of the mesencephalic tegmentum and basal diencephalon result in cortical spindling and these spindles may occasionally be synchronized, their intrinsic frequency remains fairly high. Furthermore it must be noted that most of these basal lesions are very extensive and usually encroach upon the mesial thalamus.

In the present series of experiments, the slow rhythmical ''bursts'' elicited in the non-barbiturate preparation by penicillin lesions in the thalamus have been shown to be identical to the ''deteriorated'' spindles elicitable in the barbiturate preparation by similar procedures. Therefore, the production of slow rhythmical activity in the non-barbiturate preparation cannot be purely explained as the result of a more or less local elimination of arousal influences; in fact, it also and chiefly occurs in a preparation in which these influences have been already markedly depressed (barbiturate). In addition, this effect cannot be explained as the result of a purely destructive lesion, as such a lesion is known to produce irregular delta or flattening of the cortical activity (12, 17, 23, 32, 33, 38). From what precedes, and also considering that the size of the thalamic penicillin lesion necessary to produce local or ipsilateral spindles

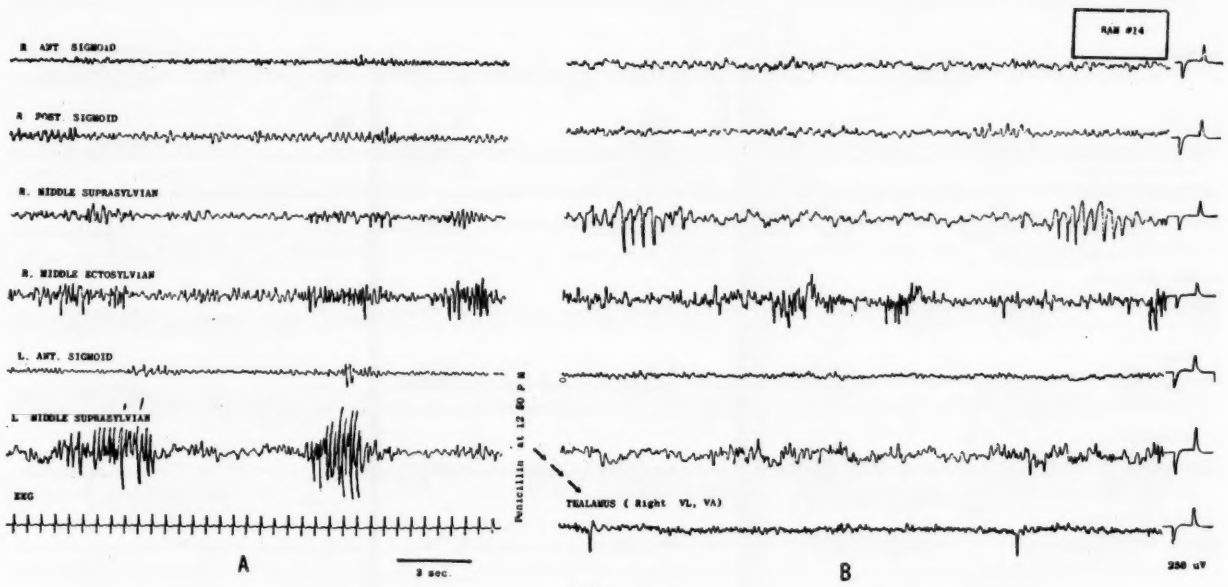


Fig. 13

A. Normal control record.

B. Presence of high voltage slow spindle in the right middle suprasylvian area with no changes in the anterior portions of the hemisphere.
Note the presence of sporadic spikes in the thalamic lead.
(For penicillin lesion see fig. 12).

may be surprisingly small, it would seem logical to conclude that these slowed bursts appearing in an otherwise alert animal, do not require inactivation of the arousal system as an explanation of the mechanism of their production.

3. *Experimental findings and human cortical rhythms.*

At the beginning of the discussion, it was stated that the 8-12 c/sec. barbiturate spindles cannot be identified with the "spontaneous cortical activity". It is also safe to state that any comparison between barbiturate spindles and the human "alpha" rhythm would meet similar if not more serious objections. There seems instead to be a somewhat closer relationship between barbiturate spindles elicitable in cat and the 11-14 c/sec. spindles seen in man during certain stages of spontaneous sleep (7, 21, 22).

The slowing of the spindles to 3.5-5 c/sec. obtained under the present experimental conditions, brings them into that range of the human rhythms generally described as rhythmical theta and rhythmical delta. These, in view of their particular topographical distribution and physiological behavior appear to be well defined electrographic entities, very unlikely related to the alpha activity (8, 15, 36, 51). There are several reasons, other than frequency identity, which may indicate that this 3.5-5 c/sec. spindle could be considered analogous to these abnormal human potentials:

(*a*) both tend to appear in fusiform bursts of amplitude higher than the background;

(*b*) both tend to appear maximally in similar cortical regions;

(*c*) both show a great tendency to synchronize. If the lesion is at the midline, the synchrony is bilateral; if the lesion is lateral.

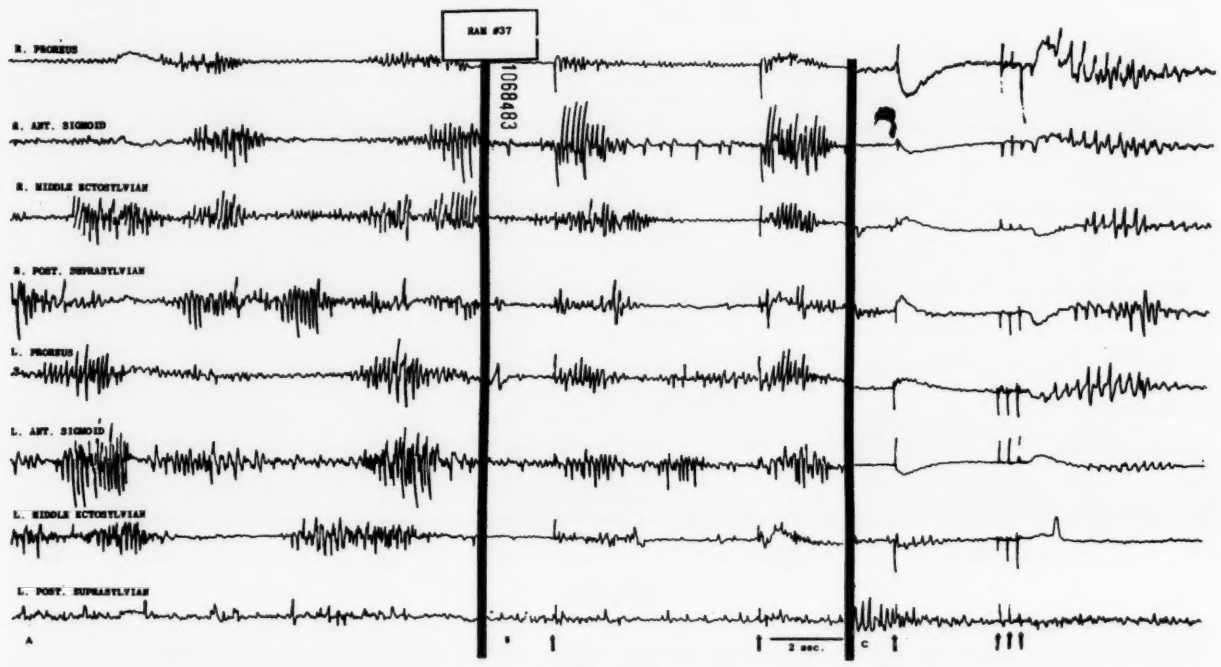


Fig. 14

A. Normal control record.

B. Response to single shock stimuli (arrow) in the right thalamus close to the midline (same placement as for penicillin lesion but before the injection).
Note the triggering of activity identical with the normal spindles on the whole right side and anteriorly on the left.

C. Response to shock stimuli 5 h. after application of penicillin in nuclei centralis medialis, paramedialis and submedius.
Although single shocks fail to elicit a response, triple shocks now trigger spindles whose shape and frequency now conform to the altered spindles produced by the penicillin.

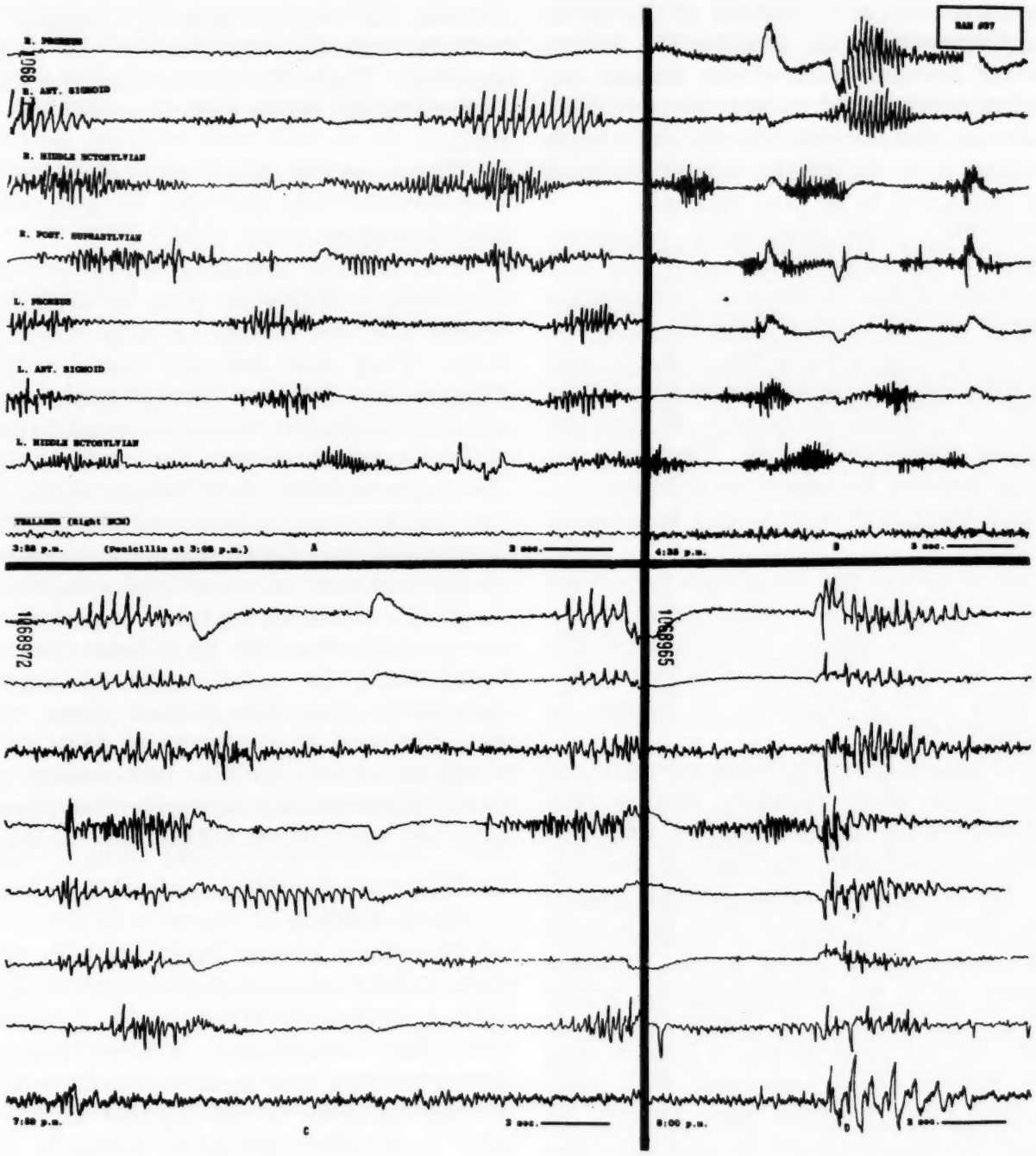


Fig. 15

A. Record 50 min. after penicillin (same lesion as in fig. 14).
Marked spindle slowing, increase in voltage and uniformity of waves in right anterior leads (the slow sway of the base line in various channels is due to a defective power supply).

B. Record 1½ h. after penicillin.

Slowing and synchronization confined to the right anterior leads.

C. Record 4½ h. after penicillin.
The spindle slowing has now extended to the opposite hemisphere but still involves anterior regions more strongly. There is now greater synchronization of the whole record and rare superimposed spiking.

D. Record shortly thereafter.
Showing increase in spiking, in cortex and thalamus, superimposed upon the markedly slowed spindles, and a greater degree of synchronization. (Note different paper speed in B).

the synchronization is ipsilateral to the lesion (the same is true of the distribution of the deteriorated spindles and of the human pathological rhythms);

(*d*) in one case the lesion is thalamic while in the other it is definitely subcortical and strongly presumed to be also thalamic.

By carrying these speculative considerations further, we might add that if the 8-12 c/sec. activity of the barbiturate preparation is analogous to the human sleep 11-14 c/sec. spindles, and if the 3.5-5 c/sec., "deteriorated" spindles of the same preparation after penicillin are related to certain rhythmical pathological potentials in man, then some relationships between human sleep spindles and paroxysmal theta and delta might be predicted. In fact:

(*a*) one is always and the others very often associated with impaired consciousness;

(*b*) both have a similar topographical distribution (maximal fronto-centro-temporal);

(*c*) both have a tendency to appear in paroxysmal bursts.

If these pathological rhythms were derived by change from sleep spindles, then a reciprocal relationship might also be expected (i.e., when one is found the other is absent). In their study on subcortical lesions, Jasper and Van Buren (30) found that in 9 cases showing during sleep 11-14 c/sec. spindles, the lesions were all extrathalamic, predominantly in the region of hypothalamus or midbrain. On the other hand, in 3 cases with impaired consciousness associated with thalamic lesions, sleep spindles were absent. In other cases the spindles were reduced ipsilateral to unilateral thalamic lesions or to lesions involving thalamo-cortical projection fibers (similar findings were also reported by others (19)). This suggested to them that sleep spindles were of thalamic origin and that subcortical lesions most likely to "spare" them involved hypothalamus or midbrain. Contrariwise, bilateral synchronous and symmetrical theta rhythm, usually maximum in fronto-temporal or fronto-central areas, was found in 12 of 17 cases with tumors involving the floor of the III ventricle or hypothalamus (one additional tumor of the septum pellucidum and fornix compressed the thalamus from above). As the lateral distance from this region increases, the cortical activity becomes asymmetrical and asynchronous on the two hemispheres. Thalamic lesions may produce an asymmetrical theta (most prominent ipsilaterally).

These results tend to confirm those of Walter (51) and are also substantiated by more recent evidence (15).

The clinical findings, therefore, suggest that sleep spindles are seen in extrathalamic lesions and are absent in large thalamic lesions. They also indicate that paroxysmal, synchronous delta or theta rhythms are prominent in lesions which encroach upon but which do not massively destroy the thalamus. The topographical distribution of the lesions and the observed pathological rhythms roughly parallel the distribution of the penicillin lesions and that of the altered spindles.

If the above interpretation and analogies are correct, then the hypothesis may be offered that the same neuronal aggregates responsible for the human sleep spindles can give rise to paroxysmal delta or theta rhythms under certain pathological conditions. The evidence suggests that these neurons are very likely within the thalamus.

4. *Experimental findings and "centrencephalic" epilepsy.*

The well known EEG picture of centrencephalic epilepsy is characterized by widespread, bilaterally synchronous, 3/sec. "wave and spike" discharges. It is of common observation that the most constant component of this complex is the regular high voltage slow wave, while the spike is highly variable and may actually disappear for a time during the "seizure". This fact has been particularly emphasized by Jasper (46, p. 590). Spikes may be present in some areas and only slow waves in others. This classical pattern forms a relatively small proportion of the total epilepsies. There is perhaps a somewhat larger group which also has characteristic electrographic features suggesting a more or less exclusive involvement of the centrencephalic system. In this group there are also paroxysmal bursts of high voltage slow waves arising from a moderately abnormal background and these are associated with spiking. However, the frequency of the discharges is less

well organized and, as a rule, slower; the synchrony less clearly defined, the spiking more irregular and the asymmetries in amplitude fairly common. In such cases, the pattern of the clinical seizures may also be of a much varied nature than in the cases of epilepsy characterized by classical 3/sec. wave-and-spike complexes, and in many cases a definite etiopathogenetic factor can also be inferred or demonstrated. We commonly refer to this last group as that of "atypical centrencephalic seizures".

Our knowledge of cortical epileptogenic lesions, either clinical or experimental, indicates that they are seldom accompanied by such an electrographic picture as above described. The epileptiform abnormalities may assume various, well known patterns but there is no indication of paroxysmal bursts of rhythmical activity or of widespread synchronization, except maybe in cases of extensive cortical (cystic) lesions (46, p. 616) in which a massive hemispheral pathology is very likely (and in such cases the synchronization is chiefly unilateral), and in some rare cases of parasagittal involvement (46, p. 606, 48).

Jasper and Droogleever-Fortuyn (28) were able to produce bilateral or unilateral synchronous slow waves of 2-300 msec. duration, by stimulation of certain regions of the thalamic non-specific system at or adjacent to the midline. These appeared best at a stimulation frequency of 3 c/sec. and were occasionally combined with a more rapid response to form a complex similar to the "wave-and-spike" of centrencephalic epilepsy. These findings suggested to the authors that a small subcortical pacemaker could account for the generalized cortical epileptic discharge which characterizes this form of epilepsy. They were, however, unable to obtain a selfsustained discharge following the period of electrical stimulation and the frequency characteristics of the recorded cortical rhythms were clearly dependent upon the rate of stimulation and could be altered by changing the same. More recently (24) similar experiments were repeated, some of the results were confirmed but in view of "many discrepancies" in regard to form, symmetry, cortical distribution, etc. of the evoked potentials, it was concluded against the theory of a brain stem "pacemaker" to explain the electrographic picture of human petit mal seizures. To date, no epileptogenic lesion has been experimentally produced which could elicit a convincing EEG petit mal pattern.

In the present series of experiments, the introduction of penicillin into the thalamus (in amounts often too small to produce a cortical "epileptogenic" focus) results in the production of synchronous bursts of high voltage, paroxysmal slow waves, their distribution depending on the localization of the lesion. Evidence has been offered to suggest that these responses are mediated through the thalamic non-specific system. Not infrequently, after several hours of recording, or usually, after the addition of more penicillin, a spiking focus is produced at the site of the thalamic electrode. When present, the spikes tend to group themselves under the synchronized spindles (fig. 4-15). An explanation for this phenomenon has been advanced by Moruzzi *et al.* (43), who showed that several types of evoked cortical activities (including strychnine spikes) were augmented during normal spindling. They attribute this effect to a "periodic waxing and waning of background excitability" of which the spindles are probably a manifestation. These spikes tend to project to the cortical areas in which the bursts of synchronized slowed spindles are occurring and they are often superimposed on these bursts. The spiking activity however, shows a somewhat greater tendency to bilateral spread than the slowed spindles when the penicillin lesion is located lateral to the midline. Occasionally the spikes may show a one to one relationship to the slow waves of the spindle but this was not a common occurrence in the lesions so far produced.

It would then seem, that a focal irritative-destructive lesion, when situated in or close to the thalamic non-specific system, can elicit most of the electrographic patterns which are considered characteristic for an "atypical centrencephalic seizure". This is true not only in an anesthetized animal, as a fully awake one will show the same type of activity, following a similar lesion. However, the preminence and extent of the abnormalities

can be markedly enhanced by barbiturates, a fact in keeping with the known clinical observation of the sensitivity of these types of epileptic disorders to (barbiturate) sleep activation (16, pp. 33 and 57).

The finding that the spike component may not appear, or requires a more extensive "stimulus" to do so, and the fact that it projects in an overlapping but wider synchronous distribution, suggests that its mechanism is somewhat dissimilar or that its origin is from a different type of neurons. Such a hypothesis might help to explain why in human pathology some non-epileptogenic lesions in subcortical structures might give rise to a bilaterally synchronous, paroxysmal theta or delta rhythm, while other lesions can produce a clinico-electrographic seizure pattern of a centrencephalic type, notwithstanding the fact that both are very likely involving the same general area.

5. *The nature of the penicillin effects and their interpretation.*

From the observation that none of the described changes are seen following the injection of comparable amounts of isotonic saline into similar thalamic loci, it would appear that the abnormal response is not simply the result of a mechanical destruction of tissue but is to be attributed to the penicillin itself (although other factors, like pH, should be considered as a possible cause). The fact that several different brands of penicillin are equally effective would exclude the possibility of an aspecific effect due to some contaminant of one particular product.

Massive thalamic lesions are known to eliminate the spindles previously induced by destruction of the mesencephalic tegmentum or subthalamus; small electrolytic thalamic lesions either produce transient or permanent slowing or depression of cortical activity and not the changes here described. It would, therefore, appear that a purely destructive lesion cannot be responsible for these changes.

Penicillin in larger amounts is known to be a highly effective epileptogenic agent (1, 31, 49, 50), and in fact, in our experiments, spiking is frequently encountered at the thalamic injection site when larger doses are used of after the drug has been left in place for several hours. Metrazol may selectively activate the thalamic "focus" even in the absence of prior spiking abnormalities.

These data make for a plausible conclusion that the minimal thalamic penicillin injections produce a mixed irritative-destructive lesion or a "potentially epileptogenic " one. Such a hypothesis would help in explaining the widespread synchronization, so similar to that elicitable by electrical stimulation of these same regions. In addition, it has been shown that the injection of acethylcholine into the cerebral ventricles may result in a slowing of the spindles, an effect which seems to be reversible with atropine (9). Such a result would not be expected if due purely to destruction.

Relatively little is known of mechanisms resulting in spindle slowing to the degree here described. Similar effects, though diffuse and generalized, have been described following heavy barbiturate intoxication (22) and/or hypothermia (34). However, these effects bear but little resemblance to the response induced by thalamic penicillin lesions: these systemic depressing factors are always associated with a generalized and marked drop in amplitude of both background activity (to almost a flat baseline) and spindle waves which become irregular and sharp. On the other hand, the slowing of the spindle intrinsic frequency with unaltered (or more often increased) voltage of the single waves, cannot be simply explained through a mechanism of "inhibition" in the sense of a selective depression and slowing of excitability and autorhythmicity of the neuronic elements (4, 47). In the case under discussion, we are likely dealing with an "altered" pacemaker: as we totally ignore the intimate mechanism through which this pacemaker works in normal conditions, we can only suggest that through some disturbing process its functioning has been "slowed down", with consequent results of slowing of the spindles, increase in voltage of the single waves, increase in their total duration and general decrease in the number of spindles per unit time. The relationship between these changes and the striking increase in synchronization remains obscure.

SUMMARY AND CONCLUSIONS

1. The injection of small amounts of penicillin into various areas of the thalamus of cats under barbiturate anesthesia is routinely followed by slowing of the 8-12 c/sec. barbiturate spindle to 3½-5 c/sec. and by spindle synchronization. Such an end result also occurs in the non-anesthetized preparation, although it may be accentuated by barbiturates.

2. The distribution of the spindle alteration depends on the location of the thalamic injection.

3. Evidence is given to suggest that these changes are mediated through the non-specific thalamic system, and that they are not necessarily dependent upon elimination of arousal mechanisms.

4. These results would confirm the hypothesis that the thalamus is very likely the anatomo-physiological substrate for the rhythmical 8-12 c/sec. barbiturate spindle and that, in regard to this particular type of electrical activity, the cerebral cortex is only secondarily activated by impulses of subcortical origin.

5. A comparison is made between the altered spindles and some human pathological rhythms commonly present in the EEG in cases of subcortical involvement.

6. The electrographic picture of some forms of "centrencephalic seizures" is described and discussed in relation to experimental findings.

7. The nature of the penicillin-induced changes is discussed.

REFERENCES

1. BORKOWSKI, W. J. and FORSTER, F. M. Convulsant effects of penicillin on the cerebral cortex. *J. Neuropatol. exp. Neurol.*, **1947**, *6*: 201-205.
2. BREMER, F. Effets de la déafférentation complète d'une région de l'écorce cérébrale sur son activité électrique spontanée. *C. R. Soc. Biol.*, Paris, **1938**, *127*: 355-358.
3. BREMER, F. Considérations sur l'origine et la nature des ondes cérébrales. *EEG Clin. Neurophysiol.*, **1949**, *1*: 177-193.
4. BREMER, F. Considération sur le problème de l'inhibition centrale. *J. Suisse de Medec.*, **1952**, *39*: 40-49.
5. BREMER, F. *Some Problems in Neurophysiology.* Univ. of London. The Athelone Press, **1953**, 26-45.
6. BREMER, F. Quelques aspects physiologiques du problème des relations réciproques de l'écorce cérébrale et des structures sous-corticales. *Acta Neurol. Psychiat. Belg.*, **1955**, *55*: 947-965.
7. CLARK, S. L. and WARD, J. W. Electroencephalogram of different cortical regions of normal and anesthetized cats. *J. Neurophysiol.*, **1945**, *8*: 99-112.
8. COBB, W. A. Rhythmic slow discharges in the electro-encephalogram. *J. Neurol. Neurosurg. Psychiat.*, **1945**, *8*: 65-78.
9. COOKE, P. M. and SHERWOOD, S. L. The effect of introduction of some drugs into the cerebral ventricles on the electrical activity of the brain of cats. *EEG Clin. Neurophysiol.*, **1954**, *6*: 425-431.
10. DEMPSEY, E. W. and MORISON, R. S. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. *Amer. J. Physiol.*, **1942**, *135*: 293-300.
11. DEMPSEY, E. W. and MORISON, R. S. The interaction of certain spontaneous and induced cortical potentials. *Amer. J. Physiol.*, **1942**, *135*: 301-308.
12. DUSSER DE BARENNE, J. G. and MCCULLOCH, W. S. Direct functional interrelation of sensory cortex and optic thalamus. *J. Neurophysiol.*, **1938**, *1*: 176-180.
13. ECHLIN, F. A., ARNETT, V. and ZOLL, J. with PECK, D. Paroxysmal high voltage and rhythmic low voltage discharges from isolated and partially isolated human cortex. *J. nerv. ment. Dis.*, **1952**, *116*: 65-72.
14. ECHLIN, F. A., ARNETT, V. and ZOLL, J. with PECK, D. Paroxysmal high voltage discharges from isolated and partially isolated human and animal cerebral cortex. *EEG Clin. Neurophysiol.*, **1952**, *4*: 147-164.
15. GASTAUT, H. The brain stem and cerebral electrogenesis in relation to consciousness. *Brain Mechanisms and Consciousness.* Blackwell, Oxford, **1954**, 249-283.
16. GIBBS, F. A. and GIBBS, E. L. *Atlas of Electroencephalography*, Vol. II. Addison-Wesley Press. Cambridge, Mass., **1952**, p. 422.
17. HANBERY, J. *Personal communication*, **1953**.
18. HANBERY, J., AJMONE MARSAN, C. and DILWORTH, M. Pathways of non-specific thalamocortical projection system. *EEG Clin. Neurophysiol.*, **1954**, *6*: 103-118.
19. HENRIKSEN, G. F., GROSSMAN, C. and MERLIS, J. K. EEG observations in a case with thalamic syndrome. *EEG Clin. Neurophysiol.*, **1949**, *1*: 505-507.
20. HENRY, C. E. and SCOVILLE, W. B. Suppression-burst activity from isolated cerebral cortex in man. *EEG Clin. Neurophysiol.*, **1952**, *4*: 1-22.
21. HESS, W. R. The diencephalic sleep center. *Brain Mechanisms and Consciousness.* Blackwell-Oxford, **1954**, 117-136.
22. HESS, R. Jr., KOELLA, W. P. and AKERT, K. Cortical and subcortical recordings in natural and artificially induced sleep in cats. *EEG Clin. Neurophysiol.*, **1953**, *5*: 75-90.
23. INGRAM, W. R., KNOTT, J. R. and WHEATLEY, M. D. Electroencephalograms of cats with hypothalamic lesions. *EEG Clin. Neurophysiol.*, **1949**, *1*: 523.
24. INGVAR, D. H. Reproduction of the 3 per second spike and wave EEG pattern by subcortical electrical stimulation in cats. *Acta Physiol. Scand.*, **1955**, *33*: 137-150.

25. JASPER, H. Diffuse projection systems: the integrative action of the thalamic reticular system. *EEG Clin. Neurophysiol.*, **1949**, *1*: 405-420.
26. JASPER, H. H. and AJMONE MARSAN, C. Thalamocortical integrating mechanisms. *Res. Publ. Ass. nerv. ment. Dis.*, **1952**, *30*: 493-512.
27. JASPER, H. H. and AJMONE MARSAN, C. *A Stereotaxic Atlas of the Diencephalon of the Cat.* The Nat. Res. Council of Canada, Ottawa, **1954**.
28. JASPER, H. H. and DROOGLEEVER-FORTUYN, J. Experimental studies on the functional anatomy of petit mal epilepsy. *Res. Publ. Ass. nerv. ment. Dis.*, **1947**, *21*: 272-298.
29. JASPER, H., NAQUET, R. and KING, E. E. Thalamocortical recruiting responses in sensory receiving areas in the cat. *EEG Clin. Neurophysiol.*, **1955**, *7*: 99-114.
30. JASPER, H. H. and VAN BUREN, J. Interrelationship between cortex and subcortical structures: clinical-electroencephalographic studies. *EEG Clin. Neurophysiol.*, **1953**, *Suppl. 4*: 168-188.
31. JOHNSON, H. C., WALKER, A. E., CASE, T. J. and KOLLROS, J. J. Effects of antibiotic substances on the central nervous system. *Arch. Neurol. Psychiat.*, Chicago, **1946**, *56*: 184-197.
32. KENNARD, M. A. Effects on electroencephalogram of chronic lesions of basal ganglia, thalamus and hypothalamus of monkeys. *J. Neurophysiol.*, **1943**, *6*: 405-416.
33. KNOTT, J. R., INGRAM, W. R. and CHILES, W. D. Effects of subcortical lesions on cortical electroencephalogram in cats. *Arch. Neurol. Psychiat.*, Chicago, **1955**, *73*: 203-215.
34. KOELLA, W. P. The influence of temperature on the electrocorticogram of the anesthetized cat. *Proc. XIX Internat. Physiol. Cong.*, Montreal, **1953**, 522-523.
35. KRISTIANSEN, K. and COURTOIS, G. Rhythmic electrical activity from isolated cerebral cortex. *EEG Clin. Neurophysiol.*, **1949**, *1*: 265-272.
36. LENNOX, M. A. and BRODY, B. S. Paroxysmal slow waves in the electroencephalograms of patients with epilepsy and with subcortical lesions. *J. nerv. ment. Dis.*, **1946**, *104*: 237-248.
37. LENNOX, M. A. and COOLIDGE, J. Electroencephalographic findings after prefrontal lobotomy. *EEG Clin. Neurophysiol.*, **1949**, *1*: 246-247.
38. LINDSLEY, D. B., BOWDEN, J. W. and MAGOUN, H. W. Effect upon the EEG of acute injury to the brain stem activating system. *EEG Clin. Neurophysiol.*, **1949**, *1*: 475-486.
39. MORISON, R. S. and BASSET, D. L. Electrical activity of the thalamus and basal ganglia in decorticate cats. *J. Neurophysiol.*, **1945**, *8*: 309-314.
40. MORISON, R. S. and DEMPSEY, E. W. A study of thalamocortical relations. *Amer. J. Physiol.*, **1942**, *135*: 281-292.
41. MORISON, R. S., DEMPSEY, E. W. and MORISON, B. R. Cortical responses from electrical stimulation of the brain stem. *Amer. J. Physiol.*, **1941**, *131*: 732-743.
42. MORISON, R. S., FINLEY, K. H. and LOTHROP, G. N. Spontaneous electrical activity of the thalamus and other forebrain structures. *J. Neurophysiol.*, **1943**, *6*: 243-254.
43. MORUZZI, G., BROOKHART, J. M., NIEMER, W. T. and MAGOUN, H. W. Augmentation of evoked electrocortical activity during spindle bursts. *EEG Clin. Neurophysiol.*, **1950**, *2*: 29-31.
44. MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.
45. MURPHY, J. P. and GELLHORN, E. Further investigations on diencephalic-cortical relations and their significance for the problem of emotion. *J. Neurophysiol.*, **1945**, *8*: 431-448.
46. PENFIELD, W. and JASPER, H. *Epilepsy and the functional anatomy of the human brain.* Little, Brown and Co., Boston, **1954**, XV, 896.
47. TERZUOLO, C. Influences supraspinales sur le tétanos strychnique de la moelle épinière. *Arch. internat. Physiol.*, **1954**, *62*: 179-196.
48. TUKEL, K. and JASPER, H. The electroencephalogram in parasagittal lesions. *EEG Clin. Neurophysiol.*, **1952**, *4*: 481-494.
49. WALKER, A. E., JOHNSON, H. C. and KOLLROS, J. J. Penicillin convulsions. The convulsive effects of penicillin applied to the cortex of monkey and man. *Surg. Gynec. Obst.*, **1945**, *81*: 592-701.
50. WALKER, A. E., JOHNSON, H. C., KOLLROS, J. J. and CASE, T. J. Effect of penicillin and other antibiotic substances on the central nervous system. *J. nerv. ment. Dis.*, **1947**, *105*: 432-435.
51. WALTER, W. G. and DOVEY, V. J. Electro-encephalography in cases of sub-cortical tumors. *J. Neurol. Neurosurg. Psychiat.*, **1944**, *7*: 57-65.

Reference: RALSTON, B. and AJMONE-MARSAN, C. Thalamic control of certain normal and abnormal cortical rhythms. *EEG Clin. Neurophysiol.*, **1956**, *8*: 559-582.

POTENTIAL WAVE MECHANISMS IN CAT CORTEX [1]

M. H. CLARE, M.A. and G. H. BISHOP, Ph.D.

Washington University Medical School, Division of Neurology, Laboratory of Neurophysiology, St. Louis, Mo.

(Received for publication: April 30, 1956)

There are two obvious paths by way of which cortical neurones may be activated. One is via axonal terminations on cell bodies. In the primary sensory projection areas, stimulation of the radiation afferents by single shocks results in a record in which brief spikes are prominent. These spikes are records of cell-body all-or-none responses, as evidenced by microelectrode recording from single neurones following similar stimulation (Tasaki *et al.* 1954). In the cortical record from electrodes one on the surface and one in white matter, these spikes appear superposed on a surface-positive wave and this is followed by a negative wave. These two wave deflections have been interpreted as the two phases of a diphasic process, indicating conduction upward along the dendrites of pyramid cells toward the cortical surface (Bishop and Clare 1953). Since the activity is initiated at or near the cell body, in a sense this process is conducted antidromically over apical dendrites.

The second type of path to cortical neurones is by way of axon terminals synapsing on dendrites themselves. Direct stimulation of the cortical surface or indirect stimulation of various paths to cortex activate the dendrites near their terminal endings in the relatively cell-free upper region of cortex, to produce a simple surface-negative wave. No cell body spikes appear in records from transcortical leads following such stimulation. Other evidence has been presented that conduction fails or is decremental along the dendrites in the dromic direction, toward the cell bodies, following single stimuli (Clare and Bishop 1955), but it may occur after repetitive stimulation.

If these two types of stimulation are applied in appropriate time relations (Jasper and Ajmone-Marsan 1950) the negative phase of the diphasic wave following stimulation of the specific thalamic radiation interferes with the simple negative wave response to dromic synaptic activation of dendrites, and vice versa. This mutual occlusion indicates that both these negative processes occur in the same elements. The cortical surface-negative wave in this instance was a recruiting wave following thalamic stimulation. This experiment thus demonstrates the activation of the same neurones by two pathways as proposed above.

The experiments to be reported here were designated to clarify the relations of the activities initiated in various paths afferent to cortex, and the contributions of these various activities to overall cortical patterns of response.

For convenient topographical reference, the classification of Rose and Woolsey (1949) has been employed. The primary projection areas of cortex are those receiving sensory (and cerebellar) radiations. The secondary projection areas are those whose destruction results in retrograde degeneration of nuclei in the thalamus other than the specific or extrinsic nuclei. The association areas in this scheme are those whose removal causes no degeneration of thalamic nuclei. Since these are poorly delimited in the cat, we use this term for those areas directly responding to stimulation of the cortical primary sensory areas (Clare and Bishop 1954; Amassian 1954). These terms are employed descriptively, without insistence on functional connotations.

[1] This work was supported in part by contract 816 (03) between the Office of Naval Research and Washington University, and in part by a grant from the Supreme Council Thirty-third Degree Scottish Rite, Northern Jurisdiction, U.S.A., through the National Association for Mental Health.

TECHNIQUE

Cats were anaesthetized with a combination of veterinary Nembutal (0.2 cc. per kg.), MgSO4 12.5 per cent (1 cc. per kg.), and ether by tracheal canula just sufficient to maintain quiescence. They were fastened to an animal board with heads fixed in a Chernak headholder. Cortical responses to thalamic or cortical stimulation and spontaneous cortical spindles of these preparations could not be distinguished from those of 3 decerebrate cats used as controls. Stimuli in thalamus were applied through an electrode assembly of two silver wires, tapered and flattened, with tip exposures of about 0.5 mm., and with a vertical separation of 1 to 1.5 mm. between tips. Also attached to the electrodes was a 75 mu steel wire employed to mark the depths of stimulation by the Prussian blue reaction following electrolysis for 30 sec. at 100μA. Manipulators for electrode placement had verniers reading in 0.1 mm. steps, and were held in ball-and-socket joints for ease of orientation. Stimulation of cortical tissue was effected through an electrode pair consisting of two wires with vertical separation of tips by 0.3 to 0.5 mm. When stimulation of only the upper fraction of cortex was desired, this electrode pair was inserted into the brain just far enough to place the upper tip exposure within the tissue. Lead electrodes were steel or silver needles insulated nearly to the tip; if tips were to be located within cortex the points were sharpened to a long taper and electrodes were inserted nearly horizontally until the tips approached the recording site. This insertion effected minimal damage to the column of tissue from which the recordings were made.

A reasonable threshold for recruiting responses from thalamic or cortical indirect stimulation, or for local direct stimulation of cortex, proved to be pulses of 2 to 3 V. discharged through a 0.01 mf. condenser with 2000 ohms plus electrode resistance in series. The electrodes were lowered until a minimum threshold for a given response (often exceeding the above value) was obtained; a voltage was then applied, usually 10 V. or more, sufficient to give a large and well-developed response at an amplification low enough to minimize the background record. As a standard procedure single shocks or groups of 2 or 3 at 5 msec. intervals were repeated usually at 6/sec., but varied in frequency as the purpose of the experiment demanded.

With electrodes of this size and separation and with strong shocks, any high degree of localization of the stimulated structures was obviously out of the question, and our aim was to obtain large responses in cortex rather than to explore sites of origin. All brains were excised and examined by the following technique. A cardboard profile of the midline hemisphere surface was prepared and an aperture cut in it to match the corpus callosum cross section. The Horsley-Clark zero plane was represented by a horizontal slit in the cardboard. The position of the optic chiasma was marked. This profile was waterproofed. After formol fixation of the brain by injection or immersion overnight a midline sagittal section was made. The profile was matched to the experimental half-brain and the horizontal plane was cut through the slit. Coronal sections were then cut by hand about 1 mm. thick, marked serially by clipping corners, etc., stained in dilute thionin in formol, rinsed in alcohol and dehydrated in three changes of acetone. After clearing in two changes of toluol they were mounted in permount between two slides and weighted to flatten. The whole preparation required about two hours.

Sections were projected and drawn to a scale of 10 times the freshly fixed preparations. On these drawings needle tracks were marked and scaled for depth at 1 cm/mm. The drawings then matched the Jasper-Ajmone-Marsan diagrams for size, and were matched for register with the appropriate cross sections of the atlas, employing such stained landmarks as lateral geniculate nucleus, ventricle, fornix, caudate, etc. The stimulus positions were then noted in terms of the nuclei as labelled. Lead needle positions in cortex were checked against measured depths of insertion obtained at the time of their removal.

After some exploration of the dorsally exposed cortex, four regions were settled on for routine recording as those most liable to give

prominent records from somewhat randomly located stimulations. These areas consisted of the optic projection area on lateral gyrus, a locus of suprasylvian lateral and anterior to the primary visual area, a locus of the middle suprasylvian just posterior to the anterior angle of that gyrus, and the somaesthetic sensory area of the posterior sigmoid gyrus. Usually two of these areas, in general adjacent ones, gave significant response to strong stimuli in one locus of thalamus. Rarely routinely applied spread widely and were not well localized as to specific point of origin.

RESULTS

I. *Incremental and decremental wave sequences in cortical response.*

Stimulation in many thalamic nuclei results in the arousal of potential wave responses defined as recruiting waves (Dempsey and Morison 1943). It is found in our experiments that cortical wave sequences with similar

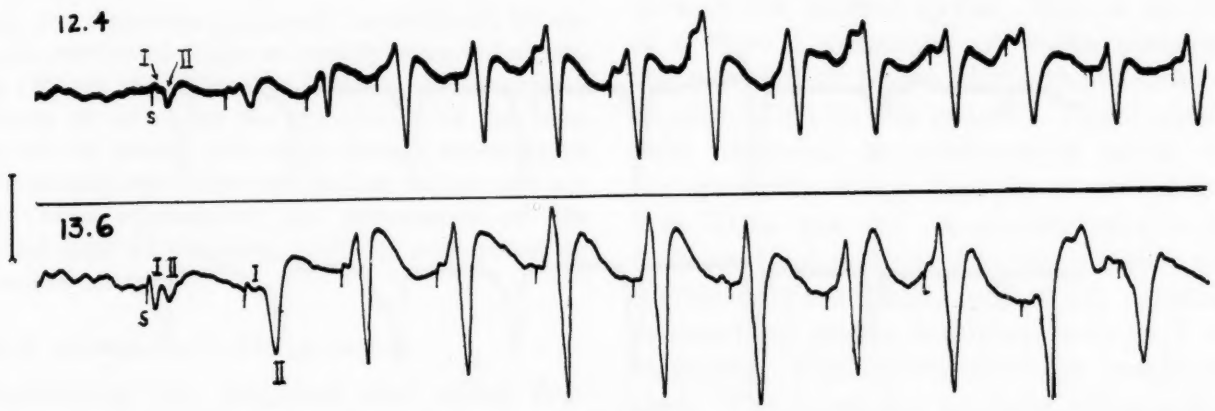


Fig. 1

Two types of waves from stimulation at 6/sec. in L.D.-M.D. of thalamus, leads across somaesthetic cortex. The lower record was from stimuli 1.2 mm. deeper than the upper, rendering the early wave more prominent. Arrows indicate positions of waves I and II. Note decrease of earlier wave, increase of later. In this figure and succeeding ones, the first stimulus artefact is indicated (s), and stimulation continues throughout records, unless otherwise noted. Voltage calibration at left 1.0 mV. Stimulation depths in mm. marked on records.

In all records, positivity at the surface electrode is recorded as an upward deflection. All leads are surface to white matter across cortex, except as noted.

both somaesthetic and visual areas responded to the same stimulus. The anterior suprasylvian area usually responded to any stimulus that activated the somaesthetic, but not always vice versa; and the same was true of the more posterior suprasylvian and optic areas. We do not think these findings are significant as defining specific projection paths from thalamus to cortex since our stimuli were strong and fibers of passage could never be excluded. On the other hand at minimal stimulation strengths the threshold responses were localized to within a few mm. and these loci of threshold responses were those which gave the largest amplitude of record following stronger stimulation. These facts confirm that our thalamic stimuli as characteristics may follow the repetitive stimulation of a distant cortical area. The critical property common to both these responses is that at certain frequencies of stimulation, optimally 6 to 10 per sec., and at constant stimulus strength, the waves progressively increase in amplitude to a maximum, then fall off somewhat to a constant but lower amplitude.

In many records from thalamic stimulation and more consistently from cortical stimulation an earlier wave appears following each stimulus. This short-latency wave has been noted previously in statements that the latency of response increased with repeated stimulation (Jasper 1949), that is, that the first wave of a sequence showed a shorter

latency than did the following waves. In many records, however, the two waves are both present in consecutive responses to stimuli. The striking difference then appears, that the earlier wave decreases as the later increases. This may occur so smoothly that the earlier becomes insignificant after the first response, while the later appears only in the second or following responses to stimuli, and the appearance is given of a sequence of single waves.

Figure 1 illustrates a repetitive sequence in which both elements are obvious. Because

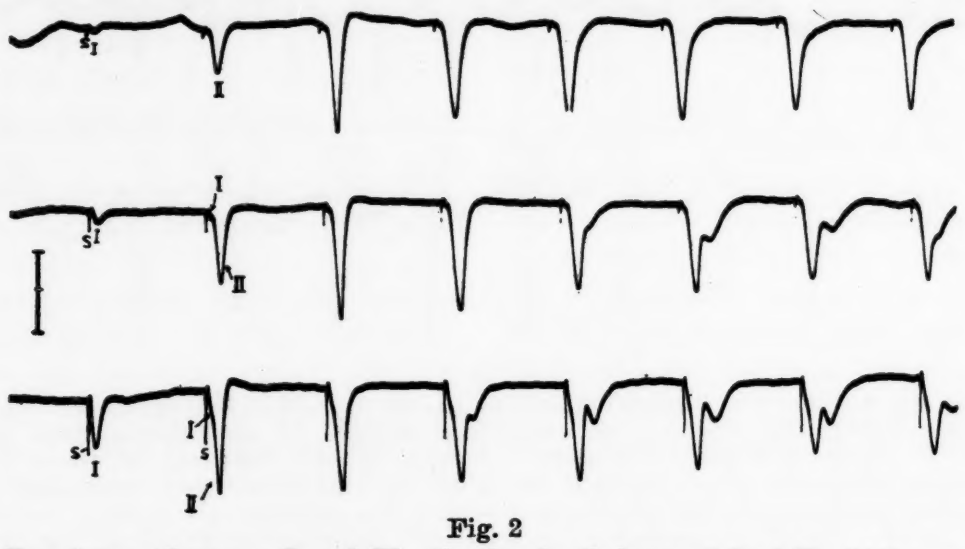


Fig. 2

Two types of waves, I and II, stimulus in thalamus L.D.-A.V., 14.2 mm. below cortical surface, stimuli 6/sec. Leads across suprasylvian cortex. Upper record, stimulus strength 4.5V., 0.01 MF. condenser. Wave I practically disappears after the first response. Middle record, 9V. stimulus, first wave persists but decreases. Lower record, 18V., first wave prominent and persists but at reduced amplitude. For a third wave in the two lower records we have no explanation; such responses are found only occasionally. Although the *apparent* thresholds for the first two waves were about the same, the later wave failed to increase with increase of voltage, although it recruited more rapidly at a higher voltage. Calibration marked in 1.0 mV. steps.

of their characteristic differences in behavior following repetitive stimulation, the earlier wave will be referred to hereafter as a decremental process, or type I response, and the longer-latency wave as an incremental or type II response, the latter including the classical recruiting waves of Dempsey and Morison (1943). While stimulation in certain loci may give rise to one or the other alone, under our experimental procedures it is more common to obtain both from the same strong stimulus; either may have the lower apparent threshold. Both types may be detected in responses to direct stimuli applied at a recording locus of cortex, where type I first appears without increment at low stimulus strengths, and type II is superposed on it at higher intensities of stimulus as an incremental component.

The class of incremental responses thus includes more than the classical recruiting waves. The differences between augmenting and recruiting waves are chiefly differences in anatomical distribution and path of activation (Dempsey and Morison, loc. cit.) but the waves appear to represent activation of similar elements.

Practically all parts of cat cortex can be excited to produce response with similar properties, and most of the thalamic cortically-dependent nuclei as well as many cortical areas serve as effective origins of the exciting impulses. Since we infer that all are the responses characteristic of dendritic activation by unmyelinated fibers, we propose to deal with them here as a single group of phenomena.

It should be recognized, however, that this type of behavior is a function of the repetitive mode of

stimulation as well as of the properties of the elements responding. That is, this rather arbitrarily applied test of repetitive stimulation does not preclude the possibility, in fact the demonstrable certainty, that the same elements can be active in other patterns of response and under other conditions than these specific experimental ones. A consistent and arbitrary test, however, serves to indentify some of the properties of this group of elements, and to differentiate them from other elements giving a different type of response. In particular it differentiates between these incremental responses included in type II and other type I responses of shorter latency which do not significantly increase under 6 per sec. stimulation, but rather usually decrease. The latter are the responses previously investigated by observing the results of single or rapidly repeated shocks at 70 to 100 per sec. (Clare and Bishop 1955) excited in one locus of cortex by the stimulation of the same or other loci of cortex. We noted there a widening of the wave during repetitive stimulation which now appears to have represented the appearance of the incremental type of response, partially superposed on the decremental type.

II. *Fiber groups activating cortex.*

Considering the latencies and other features of responses of cortex, there is evidence of four groups of fibers activating cortical neurones.

1. The fastest-conducting afferent fibers of cortex are the radiations of special sense (to primary projection areas), which in the visual system conduct at not over 50 m. per sec. (Bishop and Clare 1951). The largest fibers in the optic tract which conduct at about the same rate are 11-12 mu in diameter (Bishop and Clare 1955b).

2. A somewhat slower-conducting group is inferred from the latencies of certain cortical responses following single shock stimulation. Responses of a strip of association cortex activated by single shocks in optic cortex (Clare and Bishop 1954), occur with a latency indicating a rate of somewhere near half of the radiation rate, inexact estimates being due to short conduction distance involved. Occasional responses from stimulation in thalamic nuclei, for instance in pulvinar or posterior nucleus, indicate a similar conduction rate. The fiber sizes can only be estimated from rates as about half the 12 mu maximum of the optic tract.

Stimulation of both the above fiber groups activating cortex results in responses initiated by spikes, although these are superposed on a surface-positive wave and followed by a negative phase. The spikes must be those arising from cell bodies and their axons. We have presented evidence (Bishop and Clare 1953) for the optic cortex that the slow phases accompanying these spikes are of dendritic origin.

3. A third group of still slower fibers is activated for instance by stimulation of the lateral border of suprasylvian cortex, responses to which are recorded in the optic area of the lateral gyrus. This is an instance of a type I response. A spike assignable to the activity of these fibers themselves cannot be identified in the record. Their conduction rate, obtained by subtracting about 1 msec. for synaptic delay, figures at not more than 8 to 10 m. per sec. A similar rate is derived from cortical responses to stimulation of other cortico-cortical paths, and from certain thalamocortical paths resulting in type I cortical response. The fibers must be small myelinated. The response to their stimulation is a wave of 15 msec. duration without spikes.

4. Finally a fourth group of fibers activates recruiting and similar responses (type II) but in general not after one stimulus. The latencies of response indicate very slow conduction, and the latency depends on distance of conduction. For instance, if stimuli are applied at three loci (first, within a thalamic nucleus; second, in the internal capsule just above the ventricle; and third, in the white matter of the suprasylvian itself) and if 1 msec. for synaptic delay is subtracted from each latency of a response in the recruiting series, the remaining time is roughly proportional to the distance between stimulus and response loci along the S-shaped path from thalamus to cortex. The conduction rates figured from these times and distances are not over 1.5 m. per sec. Usually a rate of near 1 m. per sec. is found, a rate characteristic of unmyelinated fibers measured elsewhere.

Further analysis of the records of cortical responses supports this classification of fiber groupings. In the response of specific projection cortex to its sensory afferents the spike signalling the arrival of the presynaptic fiber impulse at the cortex is

clearly visible (Bishop and Clare 1951). The same applies to the second group of fibers activating association cortex following stimulation of primary projection cortex (Clare and Bishop 1954) but the spikes are all less prominent. In the cases of the type I and II dendritic responses, while we occasionally see a slight elevation preceding the slow wave, which might be a record of the incoming impulses of nerve fibers, this is always at about the cortical noise level or below it. It is for this reason

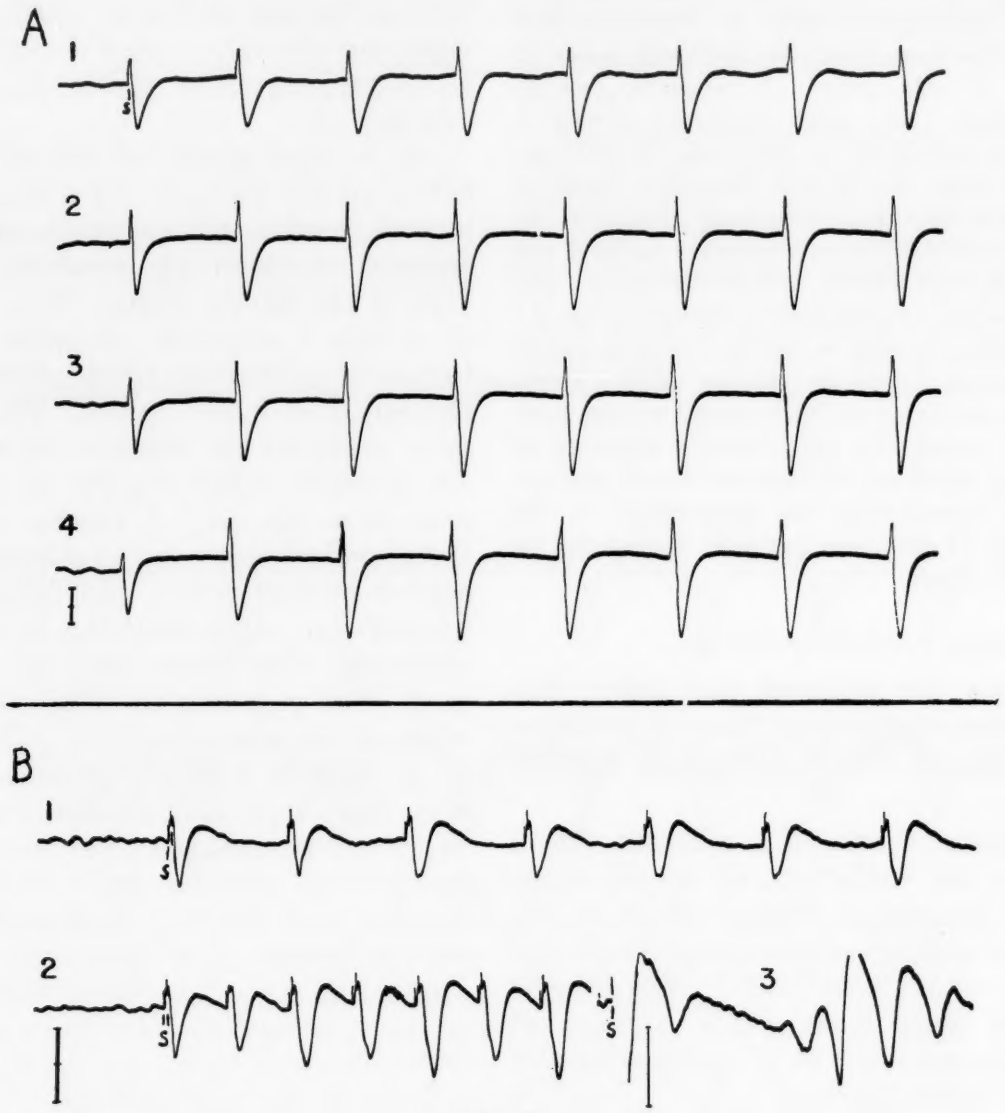


Fig. 3

(A) Recruiting responses to direct cortical stimulation, applied near surface of anterior portion of the middle suprasylvian cortex at 6/sec.; leads across cortex with surface lead within 0.5 mm. of stimulus. Record 1, 3V. stimulus, slight increment, chiefly type I response, which often fails to decrease under direct cortical stimulation, in contrast to indirect stimulation. 2, 6V., more increment of response. 3, 7.5V., and 4, 9V., show increasing recruitment, assignable to type II responses superposed on type I. No significant increase of first response of series occurs with increasing stimuli. Calibration marked in 1 mV. steps. Change in shock artifact balance (upward deflection) in first few responses is due to polarization of the stimulating electrodes.

(B) Leads across anterior portion of the middle suprasylvian, stimulated by double shocks applied 3 mm. deep below cortical surface, 6 mm. posterior to leads. Record 1, 6.5/sec., 2, 13/sec. stimulation. More frequent stimulation induces more marked recruitment of type II component; type I decreases at both frequencies. 3, a single pair of strong stimuli is followed by recruiting spindle of the same frequency as after the more optimal rate of 2. Note short latency of recruiting wave II at this conduction distance, causing superposition of two types of response but with obviously different latencies of peaks as in figure 4. Calibrations on record 2, 1 mV. steps; on 3, 0.5 mV.

that conducting times for these slow responses have been derived by subtracting a probable but unknown synapse time from the latencies of response. The same expedient had to be adopted in detecting fiber components of the optic tract (Bishop and Clare 1955b) where only the first two of four groups of fibers gave presynaptic spikes of detectable amplitude above background activity. The responses of two groups of smaller fibers activating tectal structures could not be identified directly where buried in the electrically conducting substrate of thalamic stratum zonale and colliculus.

A second criterion of fiber sizes, relative thresholds, cannot be accurately employed here as indices of diameters of the two slower groups of fibers activating cortex. In some cases the earlier of these two waves has had the lower threshold; in many others while the earlier appeared alone after a single shock near threshold, repetitive stimulation at this strength developed the later component while the earlier wave decreased to a negligible amplitude (fig. 2). A further complication, of course, is that one never knows that the different fibers eventually stimulated are at similar distances from the electrode and thus equally accessible to the current. Figure 1 records differences in relative proportions of these two responses resulting from a small change in stimulating electrode depth.

When cortex is stimulated directly, two superposed components can be distinguished as recorded close to the site of stimulation, and the earlier wave has a lower threshold than the later (fig. 3). The first of these can then be identified as a type I response by the fact that, following weak stimulation, it either decreases with 6 per sec. stimulation or fails to increase. The second component, added to the first following stronger stimuli, can be identified as a type II response by the facts that it does increase, that its duration is slightly longer than that of type I, and that its peak falls later (fig. 4). The difficulty here is that we do not know certainly whether we are stimulating directly two different groups of dendrites, or two groups of nerve fibers which excite the two postsynaptic responses in the same or different dendrites.

III. *The locus of the incremental (recruiting) function.*

For the following reasons, we infer the locus of the functions immediately determining the incremental character of the responses to repetitive stimulation to be at the cortical level, and probably at the synaptic areas of dendrites. First, stimulation of white matter in the internal capsule or even immediately beneath the cortex induces recruitment quite as does thalamic nuclear stimulation. Second, with the strong shocks from large electrodes

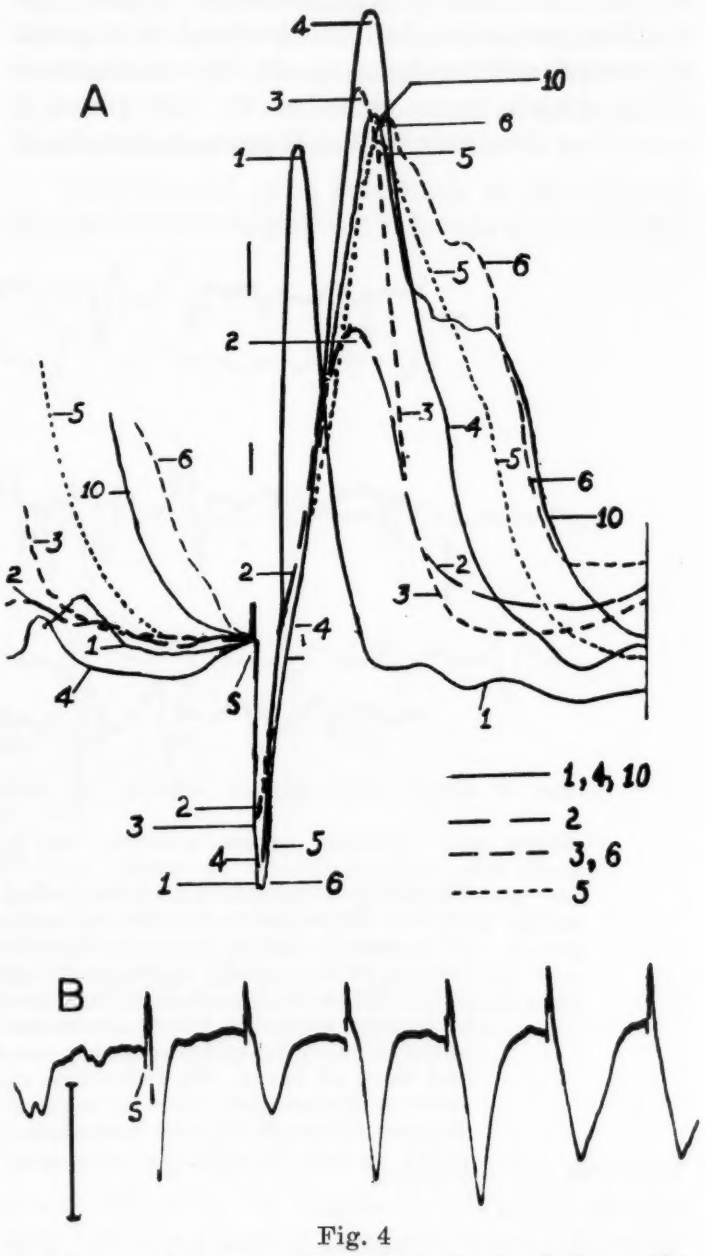


Fig. 4

Two types of response from cortical stimulation. (A) Superposed tracings, by projection, of first to sixth plus tenth responses of the recruiting series shown in (B). In the tracings surface positive is downward, and in the original strip below (B), upward as usual. Shock artefact traces were inked to project. Stimulus 9V. applied at 10/sec. just below cortex anterior to center of suprasylvian gyrus. Leads across optic area of lateral gyrus. Tracing 1, type I response only, which almost disappears in responses after the first. The initial positive deflection is shock artefact. Tracing 2, a longer-latency type II response recruits to a maximum in response 4, then falls off. In following records a further widening of the response may represent repetitive type II responses as in figure 2. Calibration on B, 1 mV.

we have employed, the axons of most of the cells in the thalamus which might respond must also be directly stimulated. We know of no properties of nerve fibers which would account for summation of effect over the successive intervals of recruitment. Third, recruiting responses can be obtained at a point of cortex within ½ mm. of the stimulated point, which is as close as we can place a recording electrode and still manage the shock artifact (fig. 3). Fourth, a cycle of excitability follows each response in a sequence of these increasing responses. After a refractory period, a hyperexcitable phase occurs at 1/6th to 1/8th sec. from the start of each wave. Supernormal excitability at this time interval accounts for the recurrent lowering of threshold to the following stimulus (see below, IV). Fifth, the interaction of a stimulated recruiting series with the spontaneously occurring 10 per sec. spindles (below, V), or with those set off by the one or more stimuli, also indicates the operation of such a cycle in both these sequences.

IV. *The character of the "recruiting" process.*

The term "recruiting", implying the addition of successively more units to an initial small number responding, may be a misleading one. The responses of the elements involved are graded responses, and a given unit that fails to respond to a first stimulus, and does respond to a second, can presumably respond to the third at a higher amplitude. The incremental responses thus presumably involve an increase of the response of each element, as well as any increase that may occur in number of elements active, as implied by the term "recruitment". In what follows we shall employ the terms recruiting and incremental as synonymous with the above reservations. The fact of either increment or

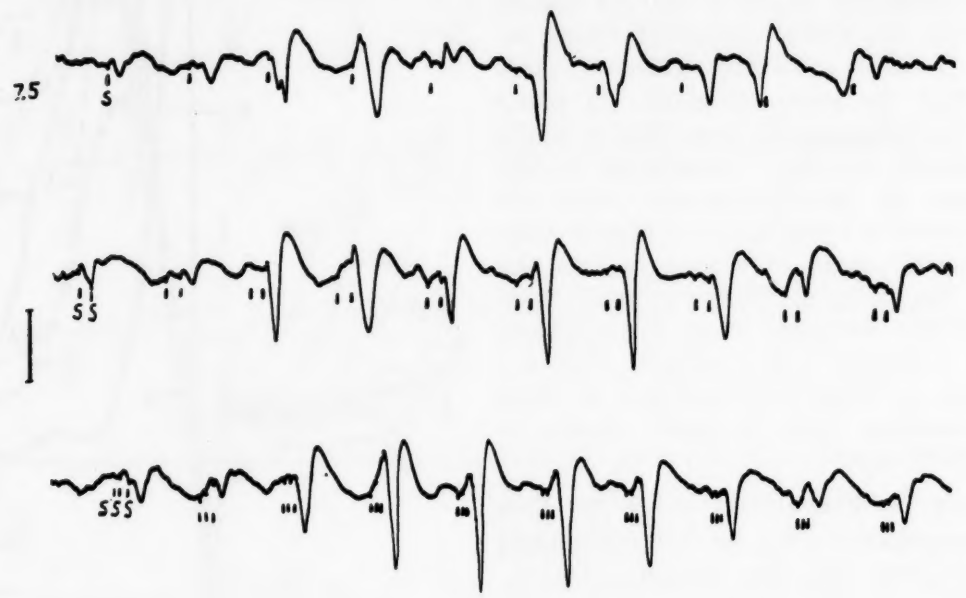


Fig. 5

Repetitive stimulation (6/sec.) using series of 2 and 3 shocks as marked by vertical lines below records, showed effects on recruitment that one shock (top record) failed to evoke effectively at this rate. Leads across anterior portion of the middle suprasylvian gyrus. Stimulation 7.5 mm. deep (tip of pair) below center of middle suprasylvian 8 mm. posterior to leads, 9V. intensity. Probably fibers from the internal capsule were stimulated. The two shocks of the middle records are spaced at the same interval as the first and third of lower. We infer that casual activity from other regions of the nervous system disturbed the regularity of the less effectively stimulated responses, although definite recruitment shows in the first four responses of the upper record, in addition to a small decremental early wave. Calibration 1 mV.

recruitment, however, involves a common factor, an increase of excitability to a synaptic excitation, and this after a long interval during which excitability is depressed.

In previous work on the visual cortex (Bishop and Clare 1952) a cycle of depression was described which was also followed by a return to normal or possibly greater excitability. The discharge at the peak of the excitable phase consisted of a barrage of waves of longer than cell spike duration, or of a more or less smoothed summation of such waves temporally dispersed. The limit of the latter summed type of response resembled an alpha wave, and the complex might be repeated at the alpha wave frequency (Bishop 1933). Such a cycle, but without a rebound above threshold, has been found in many response patterns of nervous system activity (Clare, Mills and Bishop 1951 and references there cited).

In recent work (Clare and Bishop 1955) repetitive stimulation of cortical dendrites at intervals such that each succeeding stimulus arrived *during* the previously excited 15 msec. response, showed no refractoriness during the response, and in some cases showed facilitation of the second stimulus. This phenomenon is exhibited by the recruiting responses (fig. 5 and 6). There are thus two periods during which a second stimulus can be more effective than a first, one during the first response and the second following a period of depression resulting from the response. The first situation shows true temporal summation and *supraliminal* facilitation. The second involves what might be looked on at present as a supernormal recovery phase following relative refractoriness (Forbes, Battista, Chatfield and Garcia 1949). The decremental responses fail to show such a supernormal phase.

Incremental type responses to two stimuli summate smoothly if the interval is sufficiently brief (fig. 5, 6, 7). Three shocks are still more effective. A sequence of three shocks may initiate a nearly maximal wave following a first application (fig. 8); this is maximal in the sense that succeeding waves following identical stimulation show practically no further increment. This occurs in preparations where a single first shock gives no detectable response, and two or more at 6/sec. are required to recruit a significant potential wave. From these results it may be inferred that the incremental character of the usual sequence is a result in part of the ineffectiveness of one volley from any number

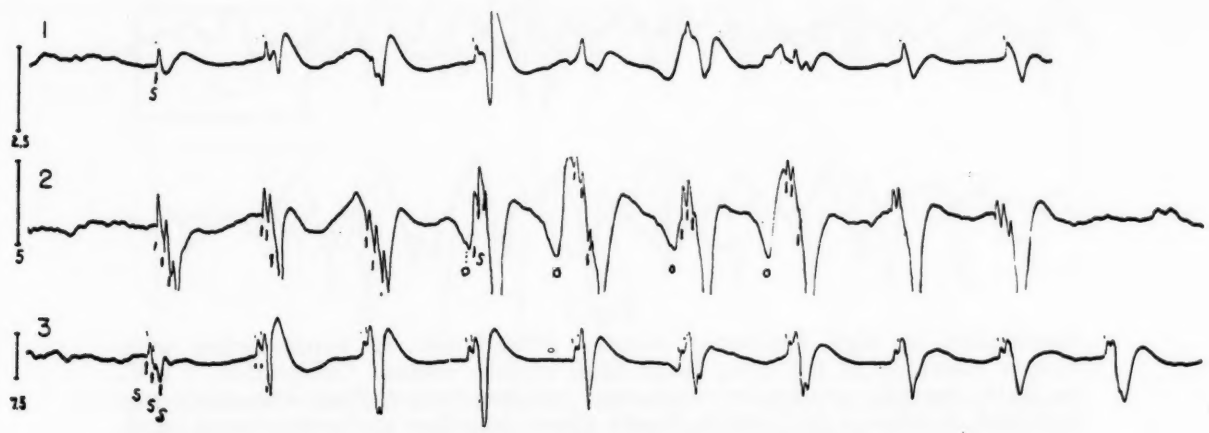


Fig. 6

Effects of high frequency stimulation. Stimulus in middle suprasylvian, leads 6 mm. anterior across cortex. All 9V. stimuli. Calibration 1 mV.
1, one shock repeated 6/sec., producing early and late potential waves, stimulus deep within cortex. In 2 and 3, the 3 dots placed under the first group of stimuli indicate the times of application of the 3 shocks. This series of 3 shocks was repeated 6/sec. during the remainder of the records. 2, stimuli 5 mm. deep in white, below locus for 1. Just before fourth response and probably before third, a spindle wave begins (marked by circles below record), its position moving earlier in the succeeding intervals, indicating the tendency to spindle arousal and the successively earlier supernormal excitability following successive responses to stimulation. 3, stimulus 7.5 mm. deep; lower amplification. Some responses show double peaks presumably due to response effects of two of the 3 stimuli.

of fibers in setting off a postsynaptic discharge.

In contrast to this requirement of rapid tetanic facilitation for *immediate* initiation of the incremental type II response, is the obvious ability of one volley to fire the type I response (fig. 1-3). The latter, while it also shows temporal summation to closely spaced stimuli, lacks the postdepression supernormality. The decremental character of type I response to 6/sec. stimulation indicates simply that depression following one response has not recovered to normal after one stimulus interval. Further, two-shock tests indicate that it shows no supernormality at any interval.

At least two other synaptic junctions are known which are characterized by this prolonged depression phase. First in the lateral geniculate synapse, complete recovery requires seconds, and no supernormality has been observed (Marshall and Talbot 1940; Bishop and O'Leary 1940). Second, we find that repetitive stimulation of the optic tract at 6/sec. results in a decreasing series of collicular potential waves, with no supernormality following depression as tested by a second shock delivered at any time after a first. The depression persists for several seconds following one stimulus, as in the geniculate synapses of myelinated fibers.

V. *Similarities between recruiting responses to stimulation and recruiting spindles.*

Similarities between recruiting responses and the spontaneous so-called barbiturate or sleep spindles (which in fact also occur in decerebrate preparations, Bremer 1949), have been noted by various workers. We have reexamined them in terms of the dendritic excitability cycle of depression and supernormality.

A. "Spontaneous" spindles initiated by one or more stimuli. In active preparations which show spindles spontaneously, a single stimulus or several at 6/sec. will start a spindle (fig. 9) which thereafter proceeds quite as do those arising spontaneously (Jasper 1949). The single stimulus effective for spindle-tripping may be so weak that no overtly observable immediate response is induced. That is, the preparation is at a high level of excitability such that a subthreshold stimulus causes a *delayed* response, occurring only after a latency of about 1/6th sec. Apparently even a subliminal increase of excitability assignable to the stimulation is followed by late supernormality. This triggering of a spontaneously increasing spindle enables one to time the occurrence of events and then to place other arbitrarily timed stimuli during the spindle in order to test the threshold during its various phases. A convenient procedure is to continue stimulation at about 6/sec. during the spindle.

A stimulus applied during one of the spontaneous spindle waves can increase its amplitude and duration. Between two spindle waves a higher threshold is found than that required for triggering the response of the

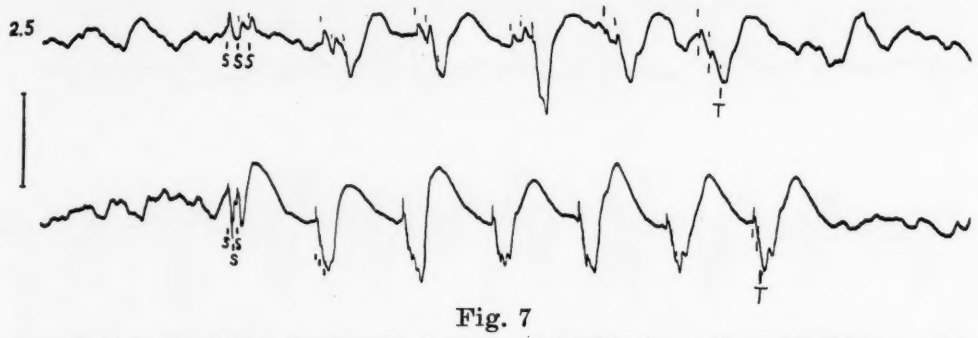


Fig. 7

Summation in high frequency bursts. Stimulation of suprasylvian with deeper electrode at 2.5 mm., leads from striate cortex. Calibration 1 mV. In both records, groups of 3 shocks (marked below first stimulus) are repeated at 6/sec. Individual shocks closer together in lower record, with greater stimulating effect, especially on late wave responses. Note reduction of spontaneous background during intervals between responses, presumably due to occlusion of activity from other paths. Last stimulus groups on each record indicated by T.

spindle. As the time for the next wave approaches the threshold decreases again to practically zero. That is, the next wave finally occurs without the stimulus. Each wave of a spindle is thus followed by an excitability cycle like that of a type II stimulated response. The successively higher responses of the spindle must be followed by successively increased supernormality, indicated both by the progressive increase of amplitude and duplicating that of the spontaneous spindle (Jasper 1949). The appearance is that of a stimulated series which itself would attain the final amplitude, but which has a spindle sequence superposed on it, and kept exactly in phase with it by the successive stimuli. Between responses the excitability is depressed as in the case of the free spindles, and late in the 1/6th sec. intervals excitability rises again, as tested by an interposed single stim-

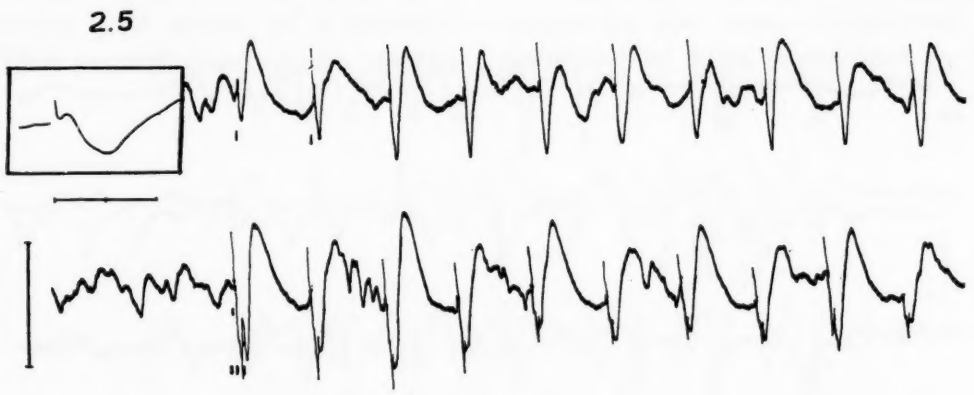


Fig. 8

Recruitment reversed to decrement by more effective stimulation. Suprasylvian stimulus, 2.5 mm. deep, 9V. Suprasylvian leads. Conduction distance via white matter 8 mm. Upper record, single stimuli repeated at 7/sec.; lower, 3 shocks, closely spaced, make the first response maximal. Calibration 1 mV. Inset at upper L., a single response at fast time, calibration in 10 msec. intervals.

The upper record appears to fall by its conduction time into the class of type I responses, which usually decrease with repetitive stimulation. This is the more striking of two such records which showed increment. At the distance conducted, a second wave should be visible if present as a widening of the total, and we cannot detect it. In lower record the repetitive shock artifacts obscure details, but total amplitude clearly decreases. We have rarely found sequences under these conditions where at least a small type II wave was not obvious following repetitive stimulation.

often by a shortening of the intervals between them.

B. The excitability cycle during a stimulated series of increasing responses. In less excitable preparations or between the occurrences of spontaneous spindles, a 6/sec. series of stimuli to an appropriate region of thalamus or cortex produces the typical incremental series. This, like the spindle, increases to a maximum, but the intervals between waves are controlled by the stimulus frequency. The maximum is followed by a decline not to zero (fig. 1 and 6), but to a constant level (Dempsey and Morison 1943). The amplitude thus follows a time course ulus. The raising and final lowering of threshold are therefore similar in the two sequences.

C. Spindles initiated during continued stimulation. If the stimulation is continued at 6/sec. in an active preparation (one in which one or a few stimuli would initiate a spindle), spindle waves appear during the stimulated sequence, one such wave following each stimulated response (fig. 6, 10).

Such a train of double responses following each shock may continue for the duration equal to that of a free spindle, or the spontaneous spindle process may take over and get out of phase with the stimulated sequences

(fig. 10). In the latter case if two waves overlap they summate, as do the responses to two stimuli applied at a short interval. If one wave falls behind the other it is depressed unless the interval approaches 1/8th sec. Thus a wave of either sequence is followed by a depressed phase that tends to occlude a wave of the other sequence.

We presume that this driving of a "spontaneous" sequence by a stimulated sequence is essentially the same as the "doubling" of response in the rabbit as observed by Fields

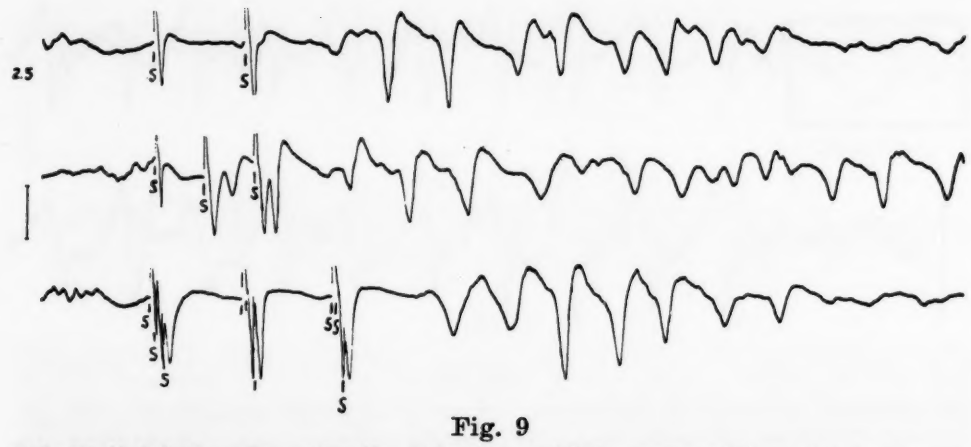


Fig. 9

Spindle initiation by stimuli. Stimulus middle suprasylvian, leads 5 mm. anterior. Upper and middle records, single stimuli repeated at 5 and 10/sec. rates, as marked below records. The first response to stimulation of each series appears to be a short-latency type I, and the second response widens and shows a later peak, to indicate the recruitment of a longer-latency recruiting response. Later waves of the second and third responses in middle record cannot be accounted for, unless they represent attempts at spindle initiation in a very active preparation. Lower record, a series of 3 shocks is repeated 3 times; first response large and apparently represents a well developed type II response which recruits. In each record, a spindle develops or persists after last stimulus. Calibration 1 mV.

duction of amplitude, although more commonly only a few such diphasic responses occurred. The diphasic waves finally became again monophasic surface-negative and of low amplitude. From the form of the waves we conclude that at a sufficient increase of excitability the elements involved conducted downward toward their cell bodies, which as far as we have been able to see does not occur in the usual preparation less intensely activated by the stimulus sequence. On cessation of stimulus these diphasic waves have ceased

et al. (1949) and King *et al.* (1953), which in that animal finally continued after cessation of stimulation as a free-wheeling paroxysm. We have not been able to induce paroxysm by our techniques in the cat but we think we have approached this.

In a few very active preparations a recruiting sequence, commencing as a series of simple surface-negative waves in response to thalamic stimulation at 6/sec., abruptly became diphasic by development of a second or positive phase almost as sharp and as high as the negative. This sequence could continue for a longer time than that of the usual spindle, and remain diphasic after the usual recruiting series would have undergone a re-

without significant afterdischarge. At least the phenomenon indicates that a high degree of excitability can be induced in these recruiting structures by strong repetitive stimulation, to the point of postponing for a time the more usual reduction of amplitude which for lack of a better term we assign to fatigue. This suggests that the ultimate effect of recruitment of these type II responses may be paroxysm. Further evidence in this direction will be presented in a study of strychnine action on recruiting responses (to be published).

D. The frequency of response in recruiting and in free spindles.

While we have used routinely as a stand-

ard 6/sec. repetitive stimulation, in our preparations a higher frequency up to 10/sec. is increasingly effective, in terms of amplitude increase of the individual waves. The reason for this is apparent if one grants that spindles are essentially self-activating recruiting responses. During the first few intervals of a spindle the frequency is usually about 6/sec., after which the frequency progressively increases up to 10/sec. or more. If stimuli are applied at a frequency of 6/sec. the first sign of a superposed spindle is seen as a small wave starting just ahead of a succeeding stimulus. This second component usually moves earlier in the interval and increases in amplitude, as a free spindle may show a shortening of the interval between responses as the sequence developes. The spindle response in the case of the stimulated sequence may move forward until it follows a stimulus response by ⅛th sec. or less peak-to-peak time. If now 8/sec. stimuli are applied, the extra responses are occluded and recruitment is more pronounced than at 6/sec. Actually the effect of specific stimulation at 8/sec. is summated and in phase with the supernormality following each previously stimulated response.

Either of two explanations might be offered for this increase of frequency during recruitment. The depression phase may shorten, and the supernormal phase then start earlier in the cycle; or the supernormality may simply increase in intensity with repeated response and thus fire earlier in its development. In the first case one would assume that depression and supernormality were the extremes of one process; in the second they might be considered to be overlapping processes which opposed each other.

E. Summary of properties of incremental responses.

All of the above relations (A to D) between free spontaneous spindles and driven incremental responses indicate that these must occur in the same structures and that the behavior of both sequences is determined by the same set of properties. Previous considerations (I-IV) indicate that the responses are those of dendrites of pyramid cells and under stimulation are activated by way of synapses from unmyelinated fibers. While we cannot exclude the possibility that recruitment such as occurs at the cortical recording locus occurs also at the stimulated loci in thalamus (Arduini and Terzuolo 1951) or in the stimulated loci of cortex at a distance from the recording site, and in fact consider *a priori* that this is probable, these cortical waves can show their usual characteristics when fiber paths in white matter are stimulated, and even following direct stimulation at the cortical surfaces. They are inferred in such cases to be functions of the cortical locus where recorded, and to be conditioned by the properties of synaptic regions. It may be that

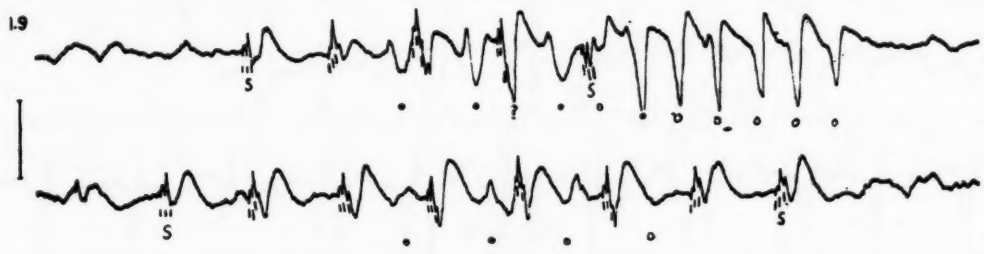


Fig. 10

Spindle responses during repetitive stimulation. Stimulus within suprasylvian cortex (deeper electrode 1.9 mm. below surface), leads 7 mm. anterior, calibration 1 mV. Groups of 3 closely-spaced stimuli are repeated 6/sec.; the first and last groups are marked. Upper record, "spindle" waves as marked with circles tend to follow stimulated responses. These fall earlier in successive intervals, finally about doubling the stimulus frequency. After the last stimulus series the spindle continues at this higher frequency. Lower record, stimulation continues through abortive spindle, in same preparation after partial fatigue. Calibration 1 mV.

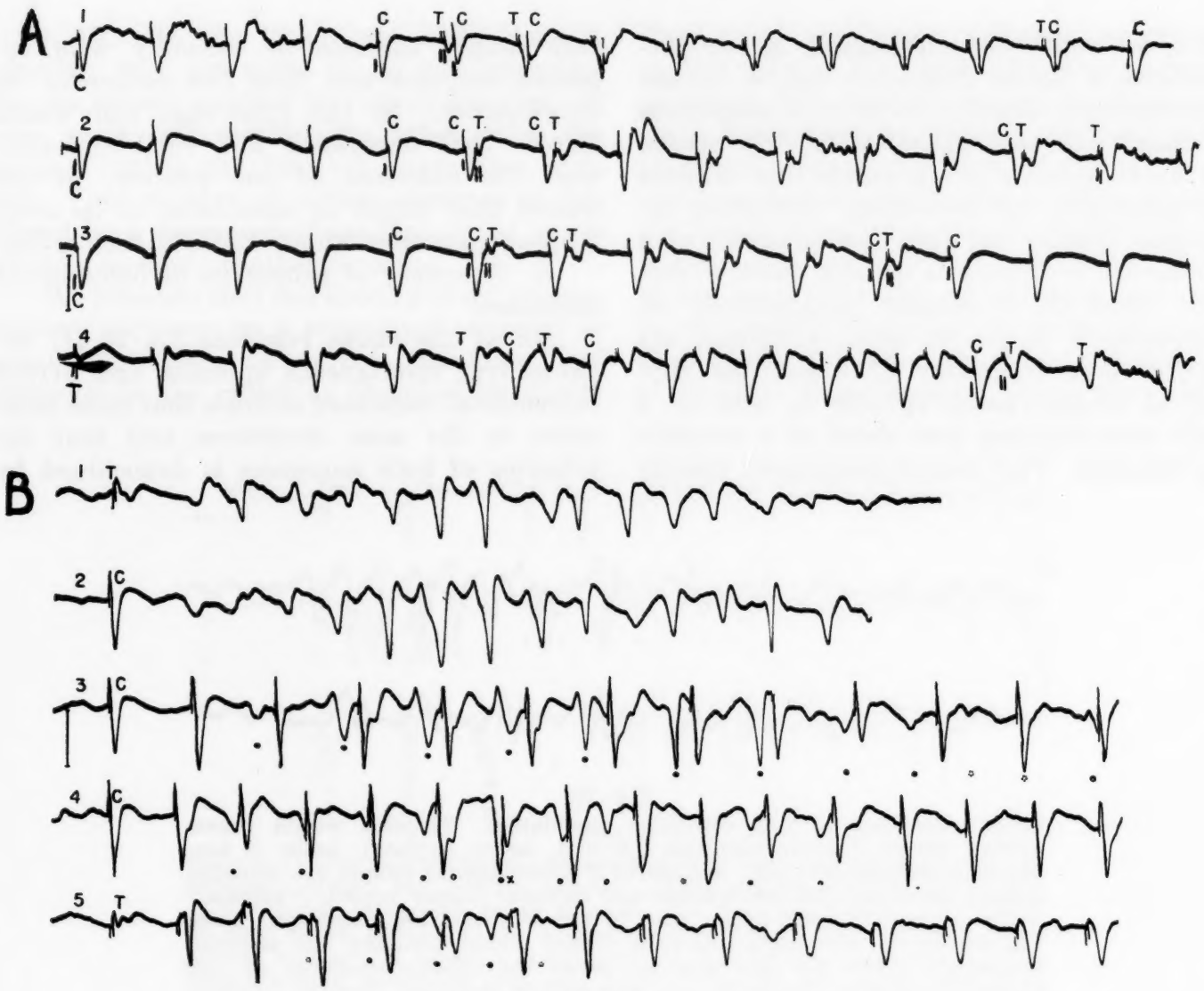


Fig. 11

(A) Interaction between responses from different paths afferent to cortex. Cortical stimulus, single shocks, 7.5 V. at 6/sec.; lower electrode 2 mm. deep within cortex of posterior area of suprasylvian gyrus. Thalamic stimulus, double shocks 15 V., 10 mm. deep at surface of pulvinar or M.D. Leads across suprasylvian gyrus 6 mm. anterior to cortical stimulus locus. Record 1, cortical stimulation (C) continues throughout record; thalamic stimuli (T) are applied ahead of cortical stimuli during the period terminated by last TC. Cortical response is depressed. 2, similar to procedure in 1, except that thalamic stimuli are applied to fall after cortical, and near end of record C is discontinued and two responses to T alone are shown. The thalamic recruiting series is depressed as compared to that at the start of record 4. 3, as in 2, but cortical stimulus, 10V., continues throughout record, and thalamic stimulus falls later after cortical during the period indicated. The same effect is induced as in 2. 4, after responses to thalamic stimulation (which continues throughout record) have levelled off in amplitude, cortical stimuli are applied about half way between thalamic stimuli. Response to thalamic stimulation is depressed by cortical stimuli but recruits slightly, and recruits again after cessation of cortical stimulation.

(B) Electrode arrangement as above. Record 1, thalamic stimuli 15V. One pair of stimuli is followed by spindle. 2, a single cortical stimulus of 7.5V. initiates spindle. 3, cortical shocks at 6.1/sec., throughout record; "spindle" waves (marked by circles) develop and die away during continued stimulation, somewhat like spontaneous spindles; i.e., the stimuli drive spindle responses. 4, same as 3 except for stimulation rate of 7.7/sec. 5, thalamic stimuli, 7.7/sec. In 4 and 5, "spindle" waves develop during continued stimulation; but unlike those developing in 3, these show variable intervals from the stimulated responses and may even sum with them (as at X in 4), as though the "spindle" sequence may become independent of the stimulated sequence. Calibration 1 mV.

the spontaneous spindles are also triggered or even driven by similar sequences in other than the locus recorded from, but we have not examined this.

VI. *Relation between incremental and decremental responses.*

It has been stated above that types I and II responses are similar in that both show summation to high frequency stimulation, and the conditions of the present work (unfortunately no technique has been developed to record from single dendrites in cerebral cortex). Occasionally regions are found whose stimulation induces one or the other of these types predominantly. In rarer instances two such stimulated regions activate one locus of cortex differently. The two sequences can then be observed separately or together in the same leads. A further requirement is that the

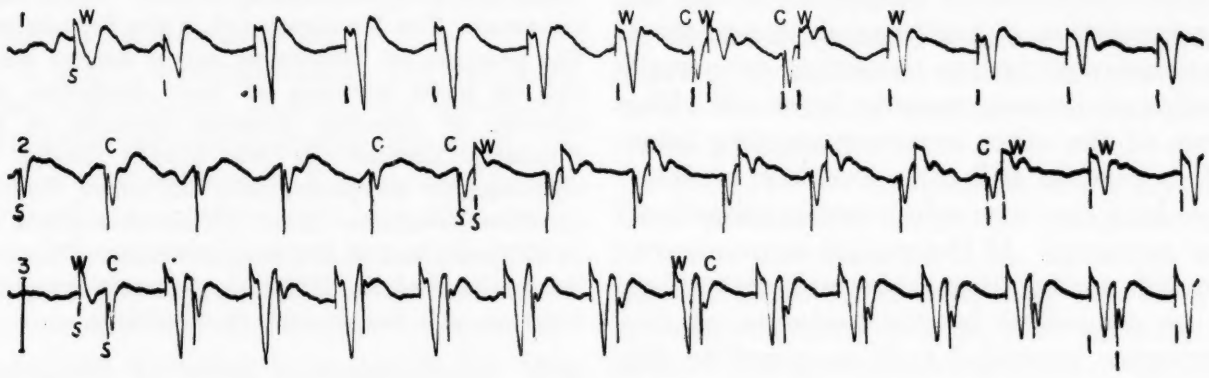


Fig. 12

Interference between response series from cortical stimulation at 25V., tip 2.2 mm. below surface of suprasylvian, 6.7/sec., and from white matter stimulation (presumably of internal capsule fibers), 10.5V., 7.5 mm. deep under lateral gyrus medial to lead locus. Leads from striate area of lateral gyrus. From anatomical considerations the two paths activated should not have included the same fibers. 1, recruiting series from deep white stimulation (W) at 6/sec. which continues throughout record; 2 cortical stimuli added (C), falling shortly before the white stimuli. Marked depression of the white stimulated responses follows cortical stimulation, with recovery when the latter is stopped. 2, cortical stimulation is continuous except for absence of last 2; as indicated, white series added at same intervals after cortical as in upper record, and persists to end of record. (First response to C shown in strip here is fourth of the stimulated sequence.) The same depression of responses to white stimulation occurs, and with apparent facilitation of responses to cortical stimulation, due to long interval W to C permitting supernormality following W to increase the responses to C. The cortical sequence alone decreases, and consists chiefly of type I responses. The deep white responses (type II) recruit strongly after cessation of cortical stimulation. 3, time relations of stimuli reversed, deep white stimulations precede cortical, and recruit sharply. Both stimuli continue throughout record. Responses to cortical stimulation decrease more rapidly than if not preceded by white (see start of 2), as white recruitment developes, then increase as amplitude of recruiting in deep white series falls off after its maximum. Calibration 1 mV.

thus show no absolute refractoriness, and that both show relative refractoriness or depression following response; and that they differ in that only the type II responses exhibit the supernormal phase that accounts for recruitment. Since their properties indicate a dendritic origin for both, the question rises whether there are two classes of dendrites involved synapsing with two types of afferent fibers, or whether both types of fibers synapse on the same dendrites but with different results.

Three tests of this could be devised within decremental sequence shall not decrease too abruptly to permit an adequate test. The coincidence of all these conditions is rare indeed, but the following tests are then possible.

First the two regions can be activated simultaneously and the degree of summation of each pair of waves examined. However, this is conclusive only if the sum of the two waves falling simultaneously is greater than the sum of responses recorded separately. Since any two non-refractory processes add completely if overlapping in time whether in the same or in different elements, 100 per

cent addition is not conclusive. The variations in these records against their background of other cortical activity renders this test equivocal.

Second, one or more stimuli of one sequence can be interposed between the responses of the other sequence. Stimulating each sequence at 6/sec., this would result in 12 responses per second, probably too high a frequency to give reliable evidence. On the other hand single stimuli are less critical than a repetitive sequence of responses which recruit on repetition. A compromise was to start one sequence well before the other, to permit amplitudes of its responses to level off. The responses of the other sequence starting later could be timed to fall either earlier or later than one half the intervals between stimuli of the first sequence. If the second sequence responses fell earlier than this midpoint, they should be depressed by the response of the first sequence, provided both occurred in the same dendrites. Figure 11 presents the effects of interference between two paths, indicating type II responses in the same locus.

A third test consisted in alternating two sequences as above but each occurring at 4/sec. and both together constituting an effective recruiting frequency of 8/sec. The results were compared with the records of each sequence at 4 and 8/sec. The refractory periods of type I responses should outlast the stimulus interval and depress type II responses; the supernormal phases of the type II responses should increase the type I responses if they affected them at all, until the type II were themselves depressed by a previous type I; whereon the type I might be expected to recover more or less. In a preliminary account (Bishop and Clare 1955a) figure 3 shows an interference which is probably of this type. A second case is presented in figure 12 herewith.

An obvious explanation of interaction between these two types of responses would be that they occupy different but not too distant regions of the same structures; and the respective properties of the two systems of responses suggest that these loci are the synaptic regions of dendrites on which two different types of fibers terminate. We can think of no other probable explanation, unless one assumes that two systems of dendrites lying parallel affect each other, either electrotonically (Gerard and Libet 1939) or by some functionally effective contact of the nature of a synapse. Certain phenomena of the spread of activity from dendrites electrically stimulated at the cortical surface during the application of strychnine at the stimulated point (to be published), would be consistent with such an hypothesis.

That different fibers may make morphologically distinctive synaptic contact on one cell is amply documented. The Mauthner cell is the best known case. The presence of boutons on spinal neuron cell bodies and on basal portions of their dendrites, with no boutons on dendritic terminal portions is another. Similarly Lorente de Nó (1934) found in the hippocampus morphologically different distributions of fiber terminals from different sources applied to different loci of the same neurones. Chang (1952) has emphasized the difference between synaptic structures on cell bodies and on dendrites.

VII. *Cortico-cortical paths of potential activation.*

When stimuli are applied to the thalamus, the responses at the cortical level tend to consist chiefly of type II slow waves; in many records no type I response is visible. When a locus of cortex is stimulated, other loci responding typically show a type I response, and in rare instances this type only or predominantly has occurred. More usually both types are present, and the first type I response of the series is the most prominent; the following I responses either decrease or fail to increase. It can be inferred from our overall experience that the type I activity, mediated via small myelinated fibers, is a much more prevalent component of cortico-cortical interaction than it is of thalamo-cortical.

The majority of our experiments involving cortical stimulation has dealt with two such paths referred to in section II, 3 and 4. Responses of cortex could be considered to be activated from other regions of cortex only if the stimulus was applied within cortex or in white matter immediately below it. More deeply placed stimuli could be expected to activate fibers from thalamus, callosum, etc.

Conduction in these two paths was definitely via subcortical white matter and not over horizontally running fibers within the

cortex itself. This was obvious when the stimulus was in white matter. Even when stimulation was within the cortex, the response arising locally fell off sharply to a distance of 3 or 4 mm., then increased in amplitude again and showed a longer latency up to 6 or more mm. distance. Whether the response recorded at 3 mm. distance or less was conducted to that distance or merely picked up as current spread from the stimulated region could usually not be determined on account of the shock artifact; no delays could be accurately measured within this distance.

For a given stimulus locus the response elsewhere was sharply localized at threshold. For activation of optic cortex the most effective stimulus locus was 2 to 4 mm. below the suprasylvian surface but laterally along the base of the cortex forming the medial wall of the suprasylvian sulcus. For activation of the anterior suprasylvian region the most effective cortical stimulus locus was in the central suprasylvian area or lateral to it, and good responses could often be obtained from the lateral border of white matter somewhat shallower than the optimum depth of stimulation for optic cortex response. By stimulation deeper in the suprasylvian white matter even larger responses could be obtained, but there the fibers stimulated could have included components from a variety of sources.

These results may have some bearing on the interpretation of the spread of activity across the cortex following sensory afferent stimulation (Lilly and Cherry 1954). Such stimulation results in responses having strong potential wave components. It seems possible that such potential wave responses might arise secondarily to the directly aroused activity at one locus and spread by way of subcortical white matter to adjacent loci, with a time sequence that is a function of distance conducted. The area finally responding might then be considerably larger than the area to which afferent impulses were primarily conducted.

DISCUSSION

1. *Significance of the recruiting type of synapse.*

The classical and presumably the primitive synapse between neurones is from axon terminal to dendrites. However, the synapse most extensively studied is that of the bouton type of ending on spinal ventral horn neurones. The one-to-one spike response across a synapse with the time interval of 0.5 to 0.7 msec. appears to be a function of a direct contact with the cell body, and the spinal ventral horn cell body itself acts in an all-or-none manner like its axon. The specific sensory response of cortex also involves cell body all-or-none response, with the short synapse time again presumably signalizing synapses on cell bodies. This type of cell body synapse then serves as a by-pass to those more primitive types of synapses on dendrites that give rise to the decremental and incremental potential waves of cortex.

The type I responses to small myelinated fiber stimulation which, as noted above, fail to show recruitment, also show no supernormal excitability following response, such as would correspond to the periodic character of the spontaneous spindle or other rythmic activity. This is most clearly demonstrable in responses of the colliculus to stimulation of the small myelinated fibers of the optic tract (above, end of section IV). The character of type II responses activated by unmyelinated fibers and the supernormal phase of excitability which follows each response must be properties of the synapses of these fibers with dendrites. Judging from the widespread occurrence of rhythmic activity in lower as well as in higher forms of animals. such synaptic properties are probably of general occurrence, and their association with unmyelinated axons may be an indication of their early origin and primitive character.

It is at least appropriate that these unmyelinated fiber synapses should predominate in an upper layer of cortex whose structural relations, of axons and dendrites making contact at a distance from the cell layers or in a relatively cell free region, are similar to the relations displayed in primitive neuropil (Herrick 1933, 1942). It is also of interest, from the point of view that these connections are primitive ones, that they predominate in certain thalamo-cortical paths, as compared to the non-incremental type of synapses of small myelinated fibers which are more prevalent in cortico-cortical paths. Such considerations warrant further study of fiber

size relations in the central nervous system comparable to the studies of functional relations of fiber size in peripheral nerves, as possible clues to the patterns of cortical organization.

We cannot say from experimental evidence that the fiber "groups" reported here are distinctly separate, rather than merely ranges in a continuous spectrum of size. The differentiation between small myelinated and unmyelinated fibers is probably discrete. Referring to the optic tract for comparison, its two first groups of fibers always show a more distinct differentiation in terms of thresholds and postsynaptic responses than can be plotted out from fiber diameter vs. numbers counted in an osmicated cross section (Bishop and Clare 1955b). The physiological differentiation of specific group limits is more equivocal with respect to two smaller postsynaptic responses recorded from the tectum; the later appears before the earlier reaches its maximum. The difficulties of analysis in dealing with small fibers buried in the conducting mass of thalamus or cortex are increased by the presence of background activity.

In addition to gross differences of latency of slow waves I and II, a range of latencies for recruiting responses, extending between 20 and 40 msec., has been recognized. Jasper (1949) has inferred that the longer latencies indicated passage through successive nuclear synapses on the route to cortex. Conduction in unmyelinated fibers available in cortex should be slow enough to account for the shorter latencies up to 20 or 25 msec.

2. *Relations between the various phenomena of cortical rhythmicity.*

It is noteworthy that either spontaneous 10/sec. spindles or stimulated recruiting waves occlude other spontaneous activity, even as they tend to occlude each other (fig. 11). It is also true that these spontaneous spindles tend to occur when the slower alpha waves are less prominent, during sleep or under soporific anaesthetics such as barbiturates, and after brainstem deafferentation. This tendency of all these activity patterns assignable to dendritic response to mutually occlude each other suggests that they all may occupy the same structures, the particular patterns depending on conditions of excitability, amount of random afferent stimulation, and on various interactions of patterns that might be applied to one locus. The fact that the same locus may show different patterns may then indicate, not that there are necessarily different sets of neurones at one locus with different properties, but also that groups of similar neurones may be activated preferentially in different patterns in the same region. Apparently if any one pattern is strongly represented it tends to dominate all or many of the neurones in that locus by occlusion of momentarily less effective activation patterns. That is, *any* of the elements present in a given region may be accessible to *each* of a variety of patterns from pathways impinging on that locus, a circumstance which is reasonable on other grounds, and the overall result in any given case will be due to the summation of, or perhaps interference between different patterns.

As a particular case, one might compare the recruiting responses, with their period of depression following each response, with the responses to stimulation of specific sensory afferents which also exhibit a depression phase following each response. In the cat, and more strikingly in the rabbit, the specific cortical response is followed by a return to at least normal excitability after an interval close to one alpha wave interval (Bishop 1933; Clare and Bishop 1952). These two patterns, alpha wave train and afterdischarge to radiation stimulation, have similar excitability cycles.

The general question may then be raised whether all such phenomena including alpha wave, alpha-like after-discharge, recruiting responses, spontaneous spindles, etc., are phenomena occupying potentially the same type of elements, but activated in different patterns. The immediate problem is, what factors might alter the frequency of repetitive discharge of such elements, which is the chief property with respect to which these various patterns differ. For instance, under anaesthesia and in otherwise inactive cortex the optimal frequency for specific stimulation of recruiting rhythmicity is higher than is the alpha frequency in a cortex complexly and randomly activated. However, the optimal frequency in a recruiting series initially, when

the intensity of response is low, tends to be at approximately the alpha rate. Again after each depression period in a sequence, the following supernormality rises successively higher, and then reaches the response level earlier, and the optimal rate of stimulation increases.

One may argue that a background of random activity may slow the optimal frequency of response. For instance, if various paths terminate on the same elements, depression and supernormal phases might be added algebraically and at random, as can be inferred from our records of specific two-path interference. This would operate to cause temporal dispersion of the activity of different elements prolonging the individual wave form, and to keep the excitability from recruiting to such a maximum as the spontaneously or stimulated high-frequency spindles exhibit. Both these factors should act in the direction of modifying a recruiting type of well-synchronized high-frequency spindles toward a pattern of the slower, dispersed type of the alpha sequence, with statistically constant amplitude.

Finally it is well known that even weak strychnine applied to the cortical surface tends to reduce other spontaneous activity. When the concentration is such that occasional single strychnine spikes fire, a prolonged state of depression follows each such spike that raises the threshold of response to stimulation of any cortical afferents investigated. On the other hand stimulation at 6 per sec. applied to cortical afferents has prevented such spontaneous firing for up to 13 sec. and probably could do so indefinitely, in strychninized cortex which had previously been firing spontaneous single spikes at one or more per second. Presumably the stimulated responses occluded the strychnine spikes.

The statement of the above relations is equivalent to saying that the excitability cycle characterizing the recruiting process is also exhibited in other potential wave patterns of activity in cortex, but that its particular expression may vary with complexity of pattern of activation. It is suggested as a tentative hypothesis that the essential features of central nervous system rhythmicity are predominantly functions of the excitability cycle of dendritic synapses, such as may be exhibited in relative isolation in the recruiting responses of apical dendrites of cortex.

SUMMARY

Evidence is presented for two types of potential-wave responses of apical dendrites of cortex. The shorter-latency of these responses decreases when its afferents are stimulated at 6 per sec. or faster, and the longer-latency process increases in amplitude.

The incremental sequences include the classical recruiting waves following thalamic stimulation, and similar responses from cortex to stimulation of other regions of cortex, or from stimulating locally at the lead position.

Four groups or size ranges of fibers activating cortex can be differentiated. The largest fibers are those of the afferent radiations to sensory primary projection areas. The next smaller activate somewhat similar responses in association area cortex when projection cortex is stimulated. A third group or division activates the decremental short-latency responses of cortex. The fourth group activates incremental or recruiting waves. From its conduction time, the latter group is inferred to consist of unmyelinated fibers.

The recruiting property appears to be a function of the excitability cycle of one type of dendritic synapse, which shows two periods of facilitation. After a first stimulus, a second is effective during the 15 msec. duration of response to the first, after which a period of depression or relative refractoriness follows. At one sixth to one tenth sec. this depression passes over into supernormal excitability. That is, the repetition of an initial stimulus causes an increased response during the supernormal phase.

Spontaneously arising recruiting spindles in nembutalized or decerebrate preparations show close resemblances to stimulated recruiting trains, and the interaction of these two sequences of waves indicates that they may occur in the same elements. In fact what are apparently waves of the spontaneous spindle type may appear during recruiting responses to repetitive stimulation if the frequency of stimulation is less than the frequency of

spontaneous spindle discharge. This phenomenon seems related to that of "doubling" of response to each stimulus during repetitive stimulation that finally passes over into paroxysmal afterdischarge.

Certain relations between incremental and decremental sequences of waves, when stimulated at different loci but recorded at the same leads across cortex, indicate that the two types of response may be those initiated at synapses via two afferent paths of different fiber types, impinging on the same dendrites.

Inferences that seem reasonable will account for the alpha rhythm and recruiting and spindle responses as processes in the same or similar elements, activated in somewhat different patterns.

REFERENCES

AMASSIAN, V. E. Studies on organization of a somesthetic association area, including a single unit analysis. *J. Neurophysiol.*, **1954**, *17*: 39-58.

ARDUINI, A. and TERZUOLO, C. Cortical and subcortical components in the recruiting responses. *EEG Clin. Neurophysiol.*, **1951**, *3*: 189-196.

BISHOP, G. H. Cyclic changes in excitability of the optic pathway of the rabbit. *Amer. J. Physiol.*, **1933**, *103*: 213-224.

BISHOP, G. H. and CLARE, M. H. Radiation path from geniculate to optic cortex in cat. *J. Neurophysiol.*, **1951**, *14*: 497-505.

BISHOP, G. H. and CLARE, M. H. Relations between specifically evoked and "spontaneous" activity of optic cortex. *EEG Clin. Neurophysiol.*, **1952**, *4*: 321-330.

BISHOP, G. H. and CLARE, M. H. Responses of cortex to direct electrical stimuli applied at different depths. *J. Neurophysiol.*, **1953**, *16*: 1-19.

BISHOP, G. H. and CLARE, M. H. Facilitation and recruitment in dendrites. *EEG Clin. Neurophysiol.*, **1955**a, *7*: 486-489.

BISHOP, G. H. and CLARE, M. H. Organization and distribution of fibers in the optic tract of the cat. *J. Comp. Neurol.*, **1955**b, *103*: 269-304.

BISHOP, G. H. and O'LEARY, J. L. Electrical activity of the lateral geniculate of cats following optic nerve stimuli. *J. Neurophysiol.*, **1940**, *3*: 308-322.

BREMER, F. Considérations sur l'origine et la nature des "ondes" cérébrales. *EEG Clin. Neurophysiol.*, **1949**, *1*: 177-193.

CHANG, H.-T. Cortical neurones with particular reference to apical dendrites. *Cold Spr. Harb. Symp. Quant. Biol.*, **1952**, *17*: 189-202.

CLARE, M. H. and BISHOP, G. H. The intracortical excitability cycle following stimulation of the optic pathway of the cat. *EEG Clin. Neurophysiol.*, **1952**, *4*: 311-320.

CLARE, M. H. and BISHOP, G. H. Responses from an association area secondarily activated from optic cortex. *J. Neurophysiol.*, **1954**, *17*: 271-277.

CLARE, M. H. and BISHOP, G. H. Properties of dendrites; apical dendrites of the cat cortex. *EEG Clin. Neurophysiol.*, **1955**, *7*: 85-98.

CLARE, M. H., MILLS, W. H. and BISHOP, G. H. Reflex factors in clonus and tremor. *J. Applied Physiol.*, **1951**, *3*: 714-731.

DEMPSEY, E. W. and MORISON, R. S. The electrical activity of a thalamo-cortical relay system. *Amer. J. Physiol.*, **1943**, *138*: 283-296.

FIELDS, W. S., KING, R. B. and O'LEARY, J. L. Study of multiplied cortical response to repetitive stimulation in the thalamus. *J. Neurophysiol.*, **1949**, *12*: 117-130.

FORBES, A., BATTISTA, A. F., CHATFIELD, P. O. and GARCIA, J. P. Refractory phase in cerebral mechanisms. *EEG Clin. Neurophysiol.*, **1949**, *2*: 141-175.

GERARD, R. W. and LIBET, B. On the unison of neurone beats. *Livro de Homenagema os Professores Alvaro e Miguel Ozorio de Almeida*, Rio de Janerio, Brasil, **1939**. pp. 288-294.

HERRICK, C. J. The amphibian forebrain. VI Necturus. *J. Comp. Neurol.*, **1933**, *58*: 1-288.

HERRICK, C. J. Optic and postoptic systems in the brain of Amblystoma tigrinum. *J. Comp. Neurol.*, **1942**, *77*: 191-353.

JASPER, H. Diffuse projection systems: the integrative action of the thalamic reticular system. *EEG Clin. Neurophysiol.*, **1949**, *1*: 405-420.

JASPER, H. and AJMONE-MARSAN, C. Thalamo-cortical integrating mechanisms. *Res. Publ. Ass. nerv. ment. Dis.*, **1950**, *30*: 493-512.

KING, R. B., SCHRICKER, J. L. and O'LEARY, J. L. An experimental study of the transition from normal to convulsoid cortical activity. *J. Neurophysiol.*, **1953**, *16*: 286-298.

LILLY, J. C. and CHERRY, R. B. Surface movements of click responses from acoustic cerebral cortex of cat; leading and trailing edges of a response figure. *J. Neurophysiol.*, **1954**, *17*: 521-532.

LORENTE DE NÓ, R. Studies on the structures of the cerebral cortex. II. Continuation of the study of the Ammonic system. *J. Psychol. Neurol.*, Lpz., **1934**, *46*: 113-177.

MARSHALL, W. H. and TALBOT, S. A. Recovery cycle of the lateral geniculate of the nembutalized cat. *Amer. J. Physiol.*, **1940**, *129*: 417-418.

ROSE, J. and WOOLSEY, C. N. Organization of the mammalian thalamus and its relationship to the cerebral cortex. *EEG Clin. Neurophysiol.*, **1949**, *1*: 391-404.

TASAKI, I., POLLEY, E. H. and ORREGO, F. Action potentials from individual elements in cat geniculate and striate cortex. *J. Neurophysiol.*, **1954**, *17*: 454-474.

Reference: CLARE, M. H. and BISHOP, G. H. Potential wave mechanisms in cat cortex. *EEG Clin. Neurophysiol.*, **1956**, *8*: 583-602.

STUDIES ON THE ADRENALINE-SENSITIVE COMPONENT OF THE RETICULAR ACTIVATING SYSTEM

ALAN BURNS ROTHBALLER, M.D.[1]

Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Institute, Montreal

(Received for publication: April 18, 1956)

Activation or "arousal" of the EEG is ordinarily thought to be brought about by stimulation of the reticular activating system; this in turn exerts a diffuse influence upon the electrical activity recorded from the entire cortex (Magoun 1954). A change in cortical electrical activity has been observed, however, in the *isolated* cortical slab after direct stimulation of the brain stem reticular formation (Ingvar 1955), and EEG activation has been produced by stimulation of the cut *peripheral* end of the splanchnic nerve (Bonvallet, Dell, and Hiebel 1954). This evidence has suggested the possible presence of a humoral or vascular phase in "arousal" or EEG activation. The possibility is further supported by the observations that both adrenaline (Bonvallet, Dell, and Hiebel 1954) and acetyl choline (Rinaldi and Himwich 1955) can bring about EEG activation when introduced into the circulation. Since acetyl choline is not ordinarily present in the blood stream, our attention was first directed to the role of adrenaline in the humoral phase of EEG activation.

Investigations of the effect of adrenaline upon the human EEG have yielded conflicting results. Some observed no effect (Gibbs, Gibbs, and Lennox 1937; Gottschalk 1952); others noted excessive beta activity (Grinker and Serota 1941) or, when frequency analysis was employed, a shift to faster frequencies (Gibbs and Maltby 1943); still others reported the appearance of slow waves (Greenblatt, Funkenstein, Miller, and Rinkel 1947; Faure 1949).

In the anaesthetized cat intravenous adrenaline produced a slight "increase in the electrical activity" of the cortex (Jasper and Erickson 1941), while in the unanaesthetized cat it produced definite EEG activation (Bonvallet, Dell, and Hiebel 1954). In the cat anaesthetized with cyclopropane increase in the electrical activity confined to the posterior hypothalamus has been reported (Porter 1952), while in the unanaesthetized guinea-pig no change was noted (Green and Morin 1953). Given systemically, adrenaline (and noradrenaline) prolonged the duration of electrographic seizures induced by applying a shock directly to the cortex (Minz and Domino 1953); applied locally to the cortex, however, it produced a marked diminution in the amplitude of the spontaneous cortical activity (Minz and Rémond 1953). Lastly, adrenaline has been observed to exert an inhibitory effect upon certain cortical synapses (Marazzi and King 1950).

It seems that adrenaline can produce a variety of central effects, many of them apparently contradictory, depending upon dose, mode of administration, particular electrical phenomenon under observation, and the manner of interpreting them.

In the following studies only a restricted group of central adrenaline actions were examined, but it is hoped that they will resolve at least some of the apparent contradictions referred to above. At the same time these studies may contribute to our understanding of the role played by adrenaline or adrenergic substances in certain functions of the central nervous system.

METHOD

The experiments were carried out on 35 cats. With a few exceptions, each animal was weighed and then anaesthetized with ether. A tracheotomy was performed and ether anaesthesia maintained by means of an attached

[1] Public Health Research Fellow of the National Institute of Neurological Diseases and Blindness.

vapor bottle. In the earlier experiments bilateral vagotomy was performed, but this was subsequently abandoned since it did not appear to modify the results.

The right sciatic nerve was prepared for stimulation, which was accomplished with a square wave stimulator connected through a stimulus isolation unit.

The left femoral vein was cannulated with a polyethylene catheter whose tip was introduced into the inferior vena cava. In the other end was inserted a needle clamped to a two-way stop-cock so that saline or various drugs could be introduced alternately into the circulation without disturbing the animal.

The left femoral artery was tied distally and cannulated with a blunt-tipped No. 18 needle. This was then attached through a short length of polyethylene tubing to a strain gauge.[1] The strain gauge was connected through a strain gauge control unit to a DC chopper-type amplifier [2] the output of which was used to drive the recording pen directly.

The muscles overlying the skull were reflected and electrodes (brass screws) introduced through the skull to the dura. After the sinuses had been unroofed one pair of electrodes was placed anteriorly on either side of the mid-line approximately over the motor cortices. The second pair was inserted through the coronal suture 2-3 cm. to each side of the mid-line while the posterior pair was located behind them, just anterior to the origin of the tentorium. Bipolar recording was carried out between the right frontal-right central, right central-right posterior, and the corresponding positions on the opposite side. The dural leads were connected to an AC amplifier and the EEG recorded on a Dynograph ink writer.

When subcortical lesions were to be made, the head was mounted in the stereotaxic apparatus after local anaesthetization of the points of contact. Otherwise the head was supported in a cloth sling in as natural a position as possible. Once the preparation was completed, the ether was discontinued and the animal immobilized with a curarizing agent; artificial respiration was carried out for the remainder of the experiment.

Subcortical lesions were made by passing a coagulating current between a pair of steel electrodes, insulated to within 1 mm. of their tips and mounted 4 mm. apart on the stereotaxic carrier. The Wyss high frequency generator was used as a current source.

Three cats were adrenalectomized beforehand. This was carried out in two stages, employing a lumbar, sub-costal approach. After the second stage, each animal was maintained on cortisone (10 mg/day, i.m.) until the day of the experiment.

Histological localization of all lesions was carried out. The blocks were fixed in formalin, mounted in paraffin and sectioned semi-serially. Alternate sections were stained with cresyl violet and Luxol blue-cresyl violet (Klüver and Barrera 1953).

DRUGS

Epinephrine hydrochloride (Adrenalin, Parke, Davis & Co.). This preparation contains approximately 99.9 per cent pure L-epinephrine and less than 0.1 per cent primary amine compound.[3] In conformity with current usage (von Euler 1951) it will be referred to as *adrenaline*. Ordinarily, the commercial preparation was diluted 1:100, so that 1 cc. contained 10 μg, although further dilutions were sometimes necessary. An attempt was made to keep the volume of solution injected relatively constant. The higher the dilution, the more rapidly the adrenaline solution was apt to deteriorate. Preservatives (such as ascorbic acid) were not used, but when working with high dilutions fresh preparations were made up frequently from the stock solution.

Levarterenol bitartrate (Levophed, Winthrop-Stearns). This is a solution of levarterenol bitartrate monohydrate but dosage is expressed as the equivalent amount of levarterenol base. Again in conformity with current usage (Von Euler 1951), it will be referred to as *noradrenaline*.

Gallamine triethiodide (Flaxedil, Pou-

[1] Pressure Transducer, Model P23-4G-255, Statham Laboratories, Beverly Hills, California.

[2] Dynograph Amplifier, Type 131, Offner Electronics Inc., Chicago, Ill.

[3] Parke, Davis & Co., Detroit, Michigan. U.S. Patent No. 2,602,818.

lenc).[1] This drug was chosen in preference to other curarizing agents for the reasons outlined by Bonvallet, Dell, and Hiebel (1954). It was given intravenously undiluted in doses of approximately 10 mg. as needed.

RESULTS

A. *Interpretation of the Cat EEG.*

Under different experimental conditions, a variety of electroencephalographic patterns were observed, ranging from low voltage fast activity to high voltage slow waves and spindles. Almost all the names which one might assign to such patterns carry with them behavioral or analytical implications which at some time or other are undesirable or inaccurate. Consequently, those patterns which it has proven useful to distinguish in the succeeding presentation have been arbitrarily assigned letters of the alphabet and are characterized below, including reference when possible to the correlation of the EEG pattern with behavior or states of consciousness (fig. 1).

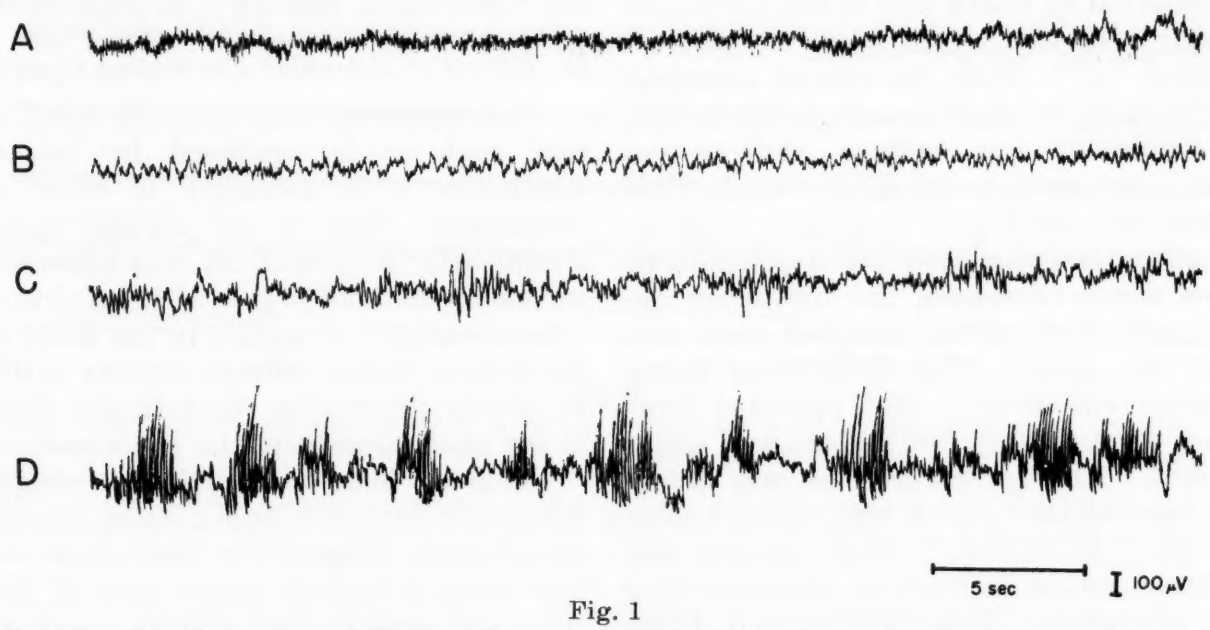


Fig. 1

Samples of various types of EEG activity observed in the unanaesthetized cat, ranging from rapid, low voltage activity (''A''), to high voltage slow waves and spindles (''D''). Preceding each pattern is an arbitrarily assigned letter of the alphabet, by which that pattern is referred to in the text.

Pattern ''A''. Immediately after a noxious stimulus, such as sciatic nerve stimulation, the EEG was characterized by very rapid activity (30-50/sec.) of intermediate voltage (50-100 μV.) and the complete absence of any slower super-imposed frequencies. It was also seen in most of the animals just as they came out of ether anaesthesia. This corresponds to the ''activation pattern'' of Rheinberger and Jasper (1937), which was described as consisting of low voltage, fast activity and was observed after a variety of external and internal stimuli all of which tended to arouse or alert the animal. For this reason, it is often referred to as the ''arousal pattern'', but it should be mentioned that its correlation with behavioural arousal, while good, is nonetheless not perfect (Wikler 1952; Hess 1954). It is also called ''desynchronization'' or ''EEG asynchrony'', but objections may be raised to both these terms, since they imply mechanisms in the generation of the EEG which have yet to be demonstrated.

Pattern ''B''. Ordinarily the EEG of the conscious and alert animal was slightly slower in frequency (25-35/sec.) and lower in voltage (20-50 μV.) than that described under ''A''. The superimposition of slower frequencies (8-20/sec.) of low voltage occurred at

[1] For which the author is indebted to Mr. W. L. Jeffry, of Poulenc Ltd., Montreal, Canada.

irregular intervals. It was seen in the intact, curarized cat after milder arousing stimuli (tactile, auditory, or visual) and was usually maintained continuously when the animal was mounted in the stereotaxic apparatus under local anaesthesia. It corresponds partly to the "activation pattern" but contains the irregular 8-16/sec. superimposed activity described by Hess, Koella, and Akert (1953) as characterizing the transition from alertness to rest, the 12-15/sec. waves observed by Rheinberger and Jasper (1937) in the relaxed animal, and the 10-15/sec. low amplitude activity reported by Clark and Ward (1945) as associated with rest.

Pattern "C". With the animal arranged as comfortably as possible and undisturbed, brief trains of low voltage slow waves (5-8/sec.) appeared in the EEG record. This state was associated with pupillary constriction, and as it progressed the amplitude of the slow waves increased, the frequency decreased, and these waves occupied more and more of the record. The underlying faster frequencies (25-30/sec.) still persisted however, but were of very low voltage and easily overlooked. Finally the record was interrupted intermittently with high voltage spindle bursts (10-14/sec.). This pattern has been described by others as characterizing rest or drowsiness (Hess, Koella, and Akert 1953) or beginning sleep (Clark and Ward 1945). We have observed it under comparable circumstances, as well as after small lesions of the reticular formation, and following the administration of chlorpromazine.

Pattern "D". This pattern never occurred spontaneously in our animals but could be produced consistently by making a lesion in the reticular formation at the ponto-mesencephalic junction. After the making of a suitable lesion, the EEG record became converted into an endless succession of spindle bursts, between which occurred intervals of high or low voltage activity of varying frequency. The record resembled the picture seen in light sleep (Hess, Koella, and Akert 1953). Often it differed slightly from the characteristic record of sleep in that the spindle bursts were more conspicuous and the slow waves less so.

In its strictest sense, the term "EEG activation" refers not to any one specific EEG pattern, but to the conversion of one pattern into another — specifically from "D" towards "A", or towards the left, if the patterns are imagined as being arranged in alphabetical order. Conversion in the opposite direction is "deactivation". Thus although the end result would not necessarily be the EEG of alert wakefulness, a change from pattern "D" to "C" is still "activation". So is the conversion from "B" to "A", even though both of these latter patterns might fall into what is generally considered the "activation pattern" to begin with.

B. *Effect of Reticular Formation Coagulation*

It is apparent that to study EEG activation such as is produced by intravenous adrenaline it is necessary to work with a preparation that is not already activated. Frequently the intact cat was unsatisfactory in this regard and it proved helpful to induce "deactivation" or a shift in the EEG toward the slower, higher voltage activity artificially by partly destroying the reticular formation at the ponto-mesencephalic junction.[1]

This was done by inserting the coagulating electrodes into the brain stem (stereotaxic coordinates: Frontal O; Horizontal —4, the tips being 2 mm. to either side of the midline) and carrying out bipolar coagulation of the area described. Immediately after making the lesion, bilateral miosis of a maximal degree (greater than that seen after section of the cervical sympathetic chain) usually appeared; the EEG showed marked activation (pattern "A"). Over the succeeding 5-15 min. the degree of EEG activation gradually lessened, the record passing through patterns "B" and "C" to "D". The succession of events differed somewhat from that seen in spontaneous drowsiness and sleep, in that the high voltage spindle bursts appeared rather abruptly, often before the appearance of much slow activity.

If the desired degree of deactivation was not obtained, it was sometimes necessary to enlarge the lesion or move the electrodes slightly anteriorly. When the electrographic

[1] The author is indebted to Dr. Robert Naquet (Marseille, France) who introduced the preparation described and demonstrated its usefulness.

activity of the two hemispheres was not symmetrical, further coagulation on the side showing less cortical deactivation was indicated. Although a lesion which produced EEG deactivation always produced miosis (provided the oculomotor nucleus was not damaged), the converse was not necessarily true.

Once the spindle activity had been properly established, the preparation showed remarkable stability. EEG activation was not produced by ordinary stimuli (touch, sound, light; olfactory or gustatory stimuli were not tried), and was produced only transiently, when at all, by sciatic stimulation, in which case the activation often barely outlasted the stimulus. Because of the preparation's insensitivity to external stimuli, it was possible to conduct the experiment under the usual laboratory conditions and without undue precautions as to noise or other disturbances, with the assurance that changes in the EEG were a consequence only of experimentally imposed stimuli and not of accidental environmental occurrences often beyond the experimenter's control. It should be added that it was the utilization of this stable but sensitive preparation which made possible semi-quantitative estimations of the effects of various drugs and procedures upon the EEG.

C. *The Effects of Sciatic Nerve Stimulation*

1. The intact, curarized animal (fig. 2)

Approximately coincident with the application of a brief (1-5 sec. duration) sciatic shock, a monophasic high voltage deflection appeared in all EEG channels and the EEG pattern was converted to that described under "A" from whatever pattern had previously been dominant. The EEG pattern faded imperceptibly into that shown under "B" over the next 10-30 sec. In those instances in which the cat ultimately reverted to the record characteristic of "drowsiness" ("C") slow waves or spindles rarely appeared before at least 40-50 sec. had elapsed. Not infrequently EEG activation persisted for several minutes, when the record was often seen to shift back and forth between patterns "A" and "B" at 10-20 sec. intervals.

A rise in blood pressure was detectable between 2 and 3 sec. after the shock; it rapidly rose to a peak and then gradually fell off over the subsequent 30-60 sec. Sometimes a second blood pressure peak or a prolonged plateau was superimposed upon the falling phase. When the rise in blood pressure occurred in two distinct phases (which was infrequent even with shocks of high intensity and short duration) a second peak of EEG activation might also be discernible coincident

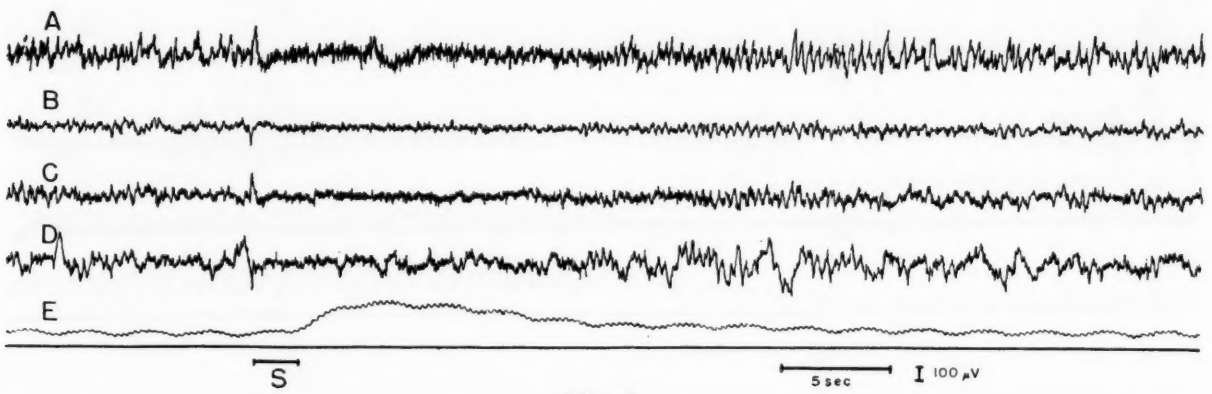


Fig. 2

This record shows the effects of a brief and relatively mild electrical stimulus ("S"), applied to the sciatic nerve, upon the EEG and blood pressure of an intact, curarized cat. Note the immediate EEG activation, and the pressor response within 2.5 sec.
Certain conventions have been observed in this and the following records (fig. 2-8). Channels A through D are bipolar recordings of the cat EEG, the electrodes having been placed on the dura: A, right frontal-right central; B, right central-right posterior; C, left frontal-left central; D, left central-left posterior. Channel E is a recording of the blood pressure; the height of the calibrating pulse ("Cal."), when present, is equivalent to 55 mm. of Hg. The continuous base-line below the blood pressure record is not at 0 but has been raised to between 60 and 90 mm. of Hg. to serve as a more convenient reference line.

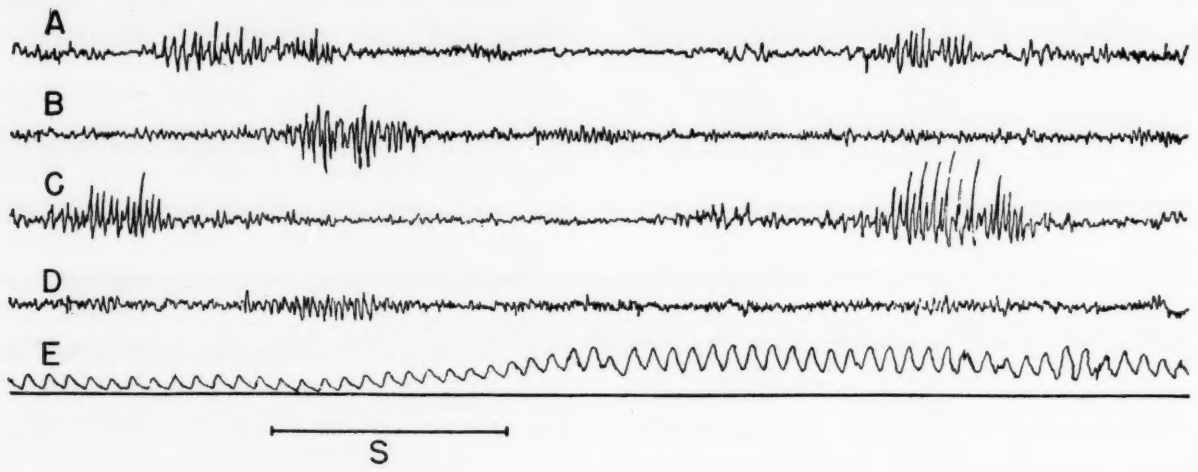
with the second blood pressure rise. Since both rises in blood pressure occurred within the first 20-30 sec. after stimulation — when EEG activation was still marked — it usually was difficult to separate the EEG pattern into distinct ''phases'' with any assurance.

2. The adrenalectomized, curarized animal

The pattern and sequence of events in the adrenalectomized animal were very similar to those described for the intact cat. The EEG activation was as intense and lasted for about as long. The blood pressure rise occurred promptly and was fully as great. However, the superimposition of a second peak or a prolonged plateau upon the falling phase was never observed; nor was a tendency observed for the EEG activation pattern or the pressor response to break up into two or more phases.

3. The animal with mid-reticular coagulation

Coagulation of the reticular formation at the ponto-mesencephalic junction was apt to have variable effects upon the response to sciatic stimulation, depending upon the exact size, symmetry and location of the lesion. (*a*) When the coagulation was small and the effect upon the EEG incomplete, i.e., conversion to the pattern described as ''C'' but not ''D'', the response to sciatic stimulation might remain quite intact. (*b*) Frequently, EEG response was only somewhat shorten



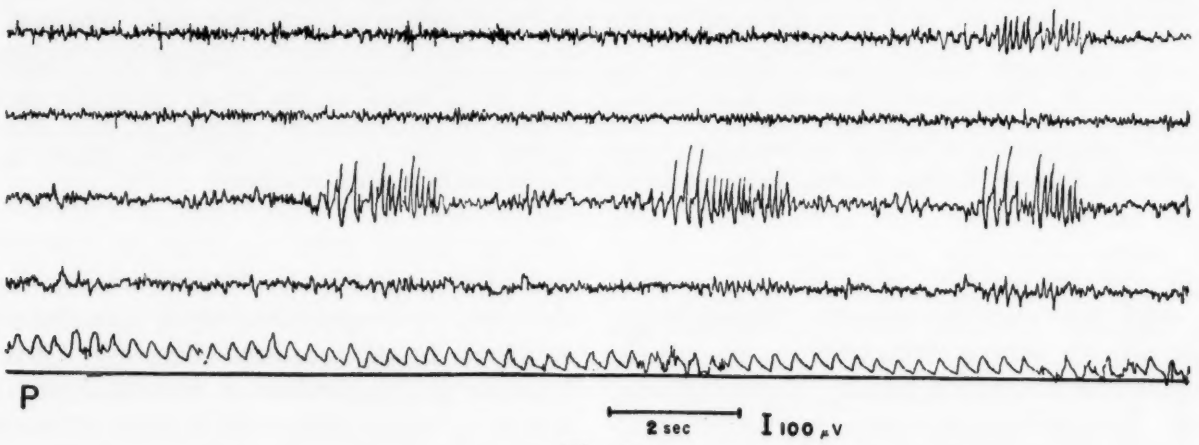


Fig. 3

The effect of sciatic stimulation after mid-reticular coagulation. EEG activation does not outlast the stimulus (''S'') and is observed only in channel A. Approximately 12-13 sec. after the beginning of the stimulus (shortly before point ''P''), a second period of activation appears in channels A, B, and D, and lasts for 16 sec. The pressor response is unchanged.

while the pressor response was completely abolished. (*c*) With more extensive lesions, the pressor response was abolished and the EEG effects were reduced to a brief effect not outlasting the stimulus or were abolished altogether. (*d*) Rarely, the pressor response would remain quite intact, but the EEG effects were *delayed*. In this last instance, the EEG activation usually appeared 12-13 sec. after the sciatic shock and lasted 15-30 sec. (fig. 3).[1]

D. *Effects of Intravenous Adrenaline Administration*

1. The intact, curarized animal.

Adrenaline was administered intravenously through a polyethylene catheter introduced into the inferior vena cava, so that the drug would enter the circulation at approximately the same site as it does normally when discharged from the adrenal glands. It was given rapidly in approximately 1 cc. amounts followed with an equal amount of physiological saline. In those instances where the animal appeared to be roused by the injection itself, saline injections were repeated until the animal ceased to respond to the procedure.

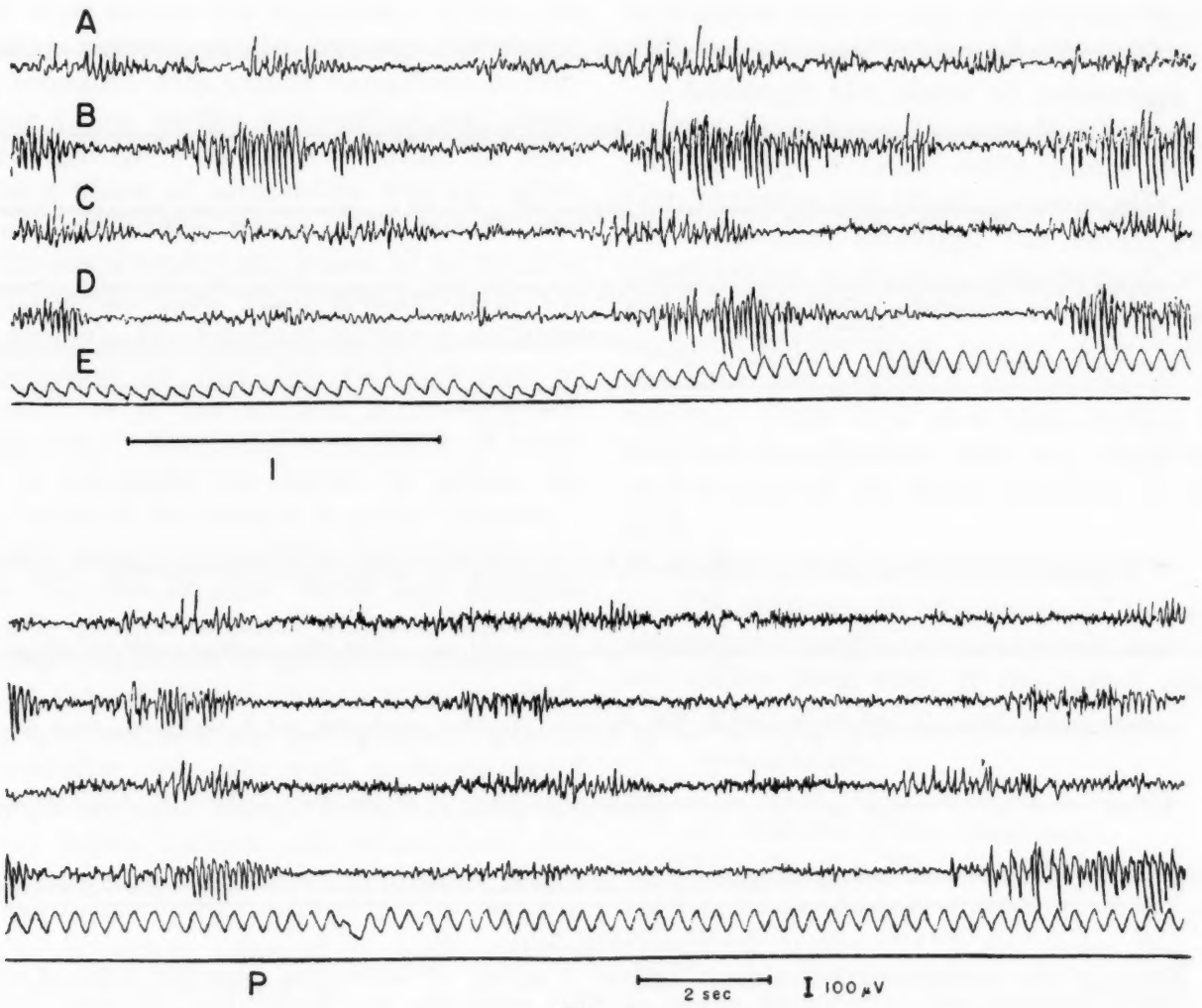


Fig. 4

Effect of the intravenous injection (''I'') of 8 μg/kg. of adrenaline in the same preparation illustrated in figure 3. This brings about EEG activation (at point ''P'') similar in appearance and timing to the second period of EEG activation shown in figure 3, indicating that the endogenous release of adrenaline could have been responsible for the late phase in figure 3.

[1] EEG activation similar in delay and duration was produced in the same animal by the intravenous administration of 8 μg/kg. of adrenaline and is illustrated in figure 4. This subject is taken up in detail in the following section.

Whether or not any EEG could be detected after intravenous adrenaline depended primarily upon the background activity and to a much lesser extent upon the dosage. Working against a background of "arousal" it was quite difficult to detect any effect at all; the most noted was a slight increase in frequency and a disappearance of some of the slower (8-20/sec.) frequencies that occur from time to time. It was often difficult to be certain about changes of so slight a magnitude and quite impossible to time or otherwise measure them. It should be emphasized that although sciatic stimulation was always able to convert "B" into "A" and thus to impose a clear-cut activation upon an already "aroused" record, adrenaline could not do so, no matter what the dosage.

Upon a background containing a certain amount of EEG "synchrony" (pattern "C"), adrenaline was capable of causing EEG activation, i.e., it produced a conversion to the "B" pattern (but never to "A"). This effect usually appeared 10-11 sec. after the beginning of the injection and was 10-40 sec. in duration.

Although EEG activation was the most conspicuous effect of adrenaline, it gradually became apparent that this was not the only effect. Under the proper circumstances, it was possible to observe the opposite effect from adrenaline, i.e., "deactivation" or an increase in high voltage slow activity, even with the appearance of spindles.

Figure 5 shows that pattern produced by 4 μg. of adrenaline in a suitable preparation.

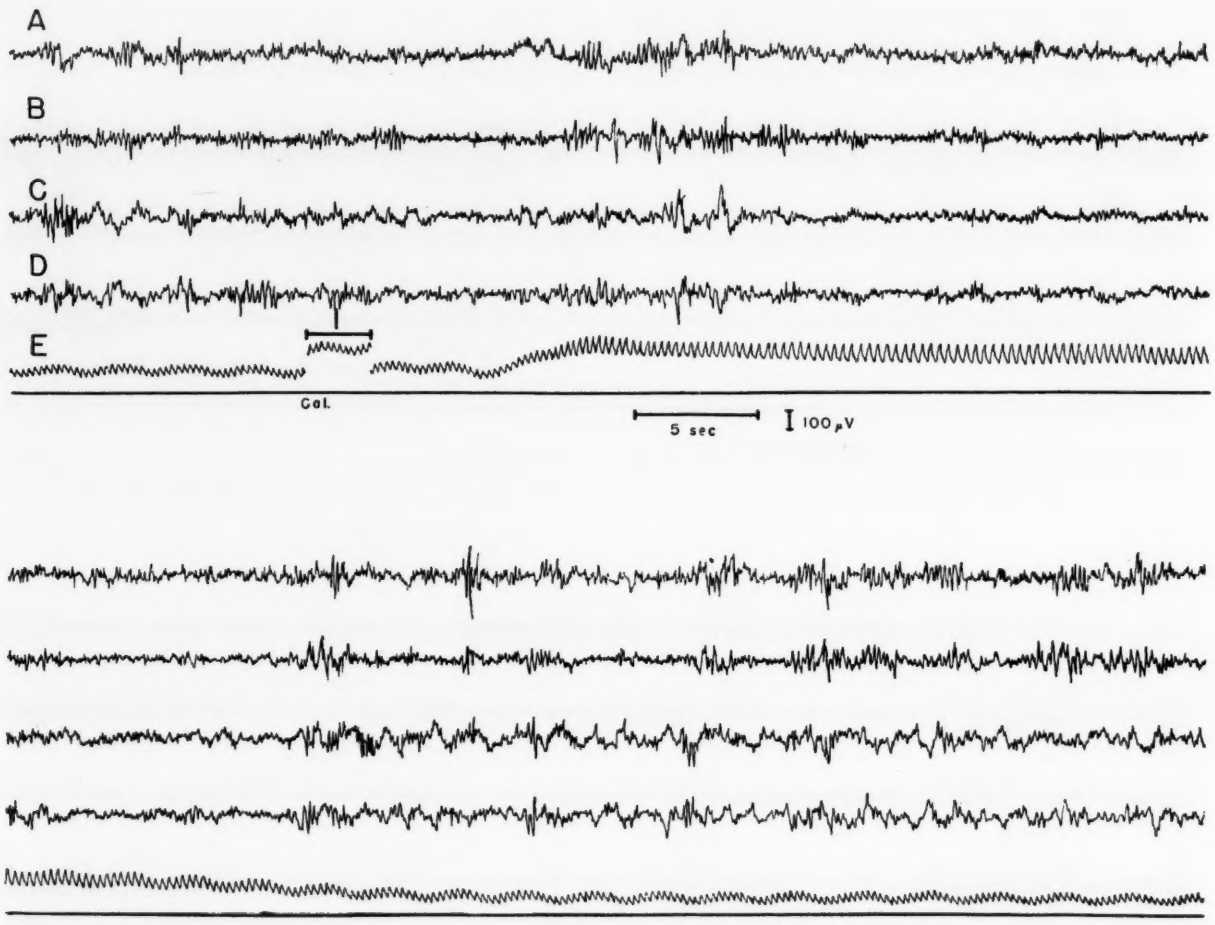


Fig. 5

Effect of the intravenous injection ("I") of 5 μg/kg. of adrenaline upon the EEG of an intact, curarized cat. Alternating phases of EEG activation and deactivation are seen. The pressor response begins at about 7.5 sec.

Between 5 and 9 sec. after the injection there was disappearance of the 5-8/sec. slow waves, revealing an underlying fast frequency of 27/sec. The slower frequencies then returned and remained until 17 sec., at which time EEG activation again supervened and prevailed until 48 sec. after the beginning of the injection, when the record reverted back to that seen before the injection. While this particular pattern might appear fortuitous, it was repeated with minor variations in timing four times in the succeeding half hour.

Although the very early (within 5-9 sec.) excitatory phase of adrenaline was not often seen, an inhibitory phase both before and after the main excitatory phase of adrenaline was almost the rule when dealing with the intact animal. Its detection however requires a preparation in just the right degree of "arousal" — if the animal is too aroused (pattern "A") the inhibitory effect of adrenaline is generally too feeble to affect the record, while if the animal is quite "drowsy" and shows considerable EEG hypersynchrony a slight increase in slow waves and spindles may easily pass unnoticed. In some instances adrenaline produced a series of alternating phases of activation and deactivation gradually approaching the pre-adrenaline level of EEG activity. In cats with a background activity of the "B" type, where it is difficult to detect much further activation from adrenaline, the deactivation or inhibitory phase often appeared quite clearly 40 or 50 sec. after the injection, ushered in with sudden spindle bursts and slow waves.

The smallest amount of adrenaline able to produce a clear-cut EEG effect was 2 μg/kg.; The usual dose was 5-8 μg/kg., and little was to be gained by exceeding this. Since, as mentioned above, minimal responses are difficult to quantify in the intact animal, no attempt was made to find the threshold dose.

Under the above circumstances, adrenaline initiated an abrupt rise in blood pressure beginning 7-8 sec. after the onset of the injection, and lasting a variable period thereafter, depending upon the dose. Smaller amounts of adrenaline produced a rather small rise in blood pressure followed by a longer fall.

In summary, intravenous adrenaline produces a series of alternating periods of EEG activation and deactivation. Shortly after the injection, when the blood and brain content of adrenaline are presumably rising rapidly, these phases are passed through quickly and may be missed, the record assuming the dominant activated pattern. Then as the adrenaline level slowly falls, the activated pattern gives way to one of alternate activation and deactivation or that of deactivation alone.

Although the phase of activation usually follows by 4-5 sec. the rise in blood pressure, occasionally a brief early phase of activation *precedes* the blood pressure rise (see fig. 5). Likewise, although the early phase of deactivation is usually synchronous with the onset of the blood pressure rise, the late phase of deactivation often occurs when the blood pressure has returned to normal or is subnormal. Thus it is seen that neither activation nor deactivation bear any fixed relation to the level of the blood pressure or changes in it.

2. The adrenalectomized animal.

The response to adrenaline of the adrenalectomized, cortisone-maintained animal did not differ from that of the intact animal.

3. The animal with mid-reticular coagulation.

(a) Pattern of the Response

Depending on the extent of coagulation, such animals showed either the EEG pattern described under "C" or, more frequently, that under "D". When the amount of coagulation was small and pattern "C" predominant, the effects of adrenaline were in all respects comparable to those observed in the intact, spontaneously drowsy animal showing a similar EEG background; both the activation and deactivation phases were observed.

With more extensive lesions in the reticular formation, the background pattern was that described under "D". In such animals it was impossible to detect any phase of deactivation, presumably because the background was already that of maximum high voltage slow activity. As a result, the phase of EEG activation stood out very clearly, being marked by a rather abrupt cessation

of spindles and slow waves and the appearance of fast, low voltage activity (usually pattern "B"). Activation characteristically appeared 8-14 sec. after the beginning of the injection of a moderate dose of adrenaline and lasted from 40-80 sec. At the end of the response, spindles and slow activity abruptly reappeared, so that there was no difficulty detecting the response or timing it (fig. 6).

The effect of adrenaline upon blood pressure in the animal with mid-reticular coagulation was no different from that in the intact animal, and the coagulation procedure itself did not change the blood pressure.

(*b*) *Adrenaline Threshold*

Because of the clear-cut nature of the activation response and the stability of such a preparation over many hours, it was possible to reduce the adrenaline dosage progressively in an attempt to determine the threshold. Typical results are illustrated in the protocol from an 4 kg. male cat (RC 28) subjected to mid-reticular coagulation:

Adrenaline i.v.	*Beginning and end of EEG activation (in sec. after onset of injection)*	*B.P. response*
15.0 μg.	9-60 sec.	rise at 7.5 sec.
5.0 "	10-47 "	" "
2.5 "	10-45 "	" "
2.0 "	13-42 "	" "
1.0 "	10-28 "	" "
0.5 "	9-24 "	" "
0.25 "	12-23 "	fall at 18 sec.
0.20 "	23-38 "	" 20 "
0.15 "	no effect	no effect

Thus as smaller and smaller doses of adrenaline were given, the period of activation characteristically became shorter and shorter but its time of onset for any one cat changed

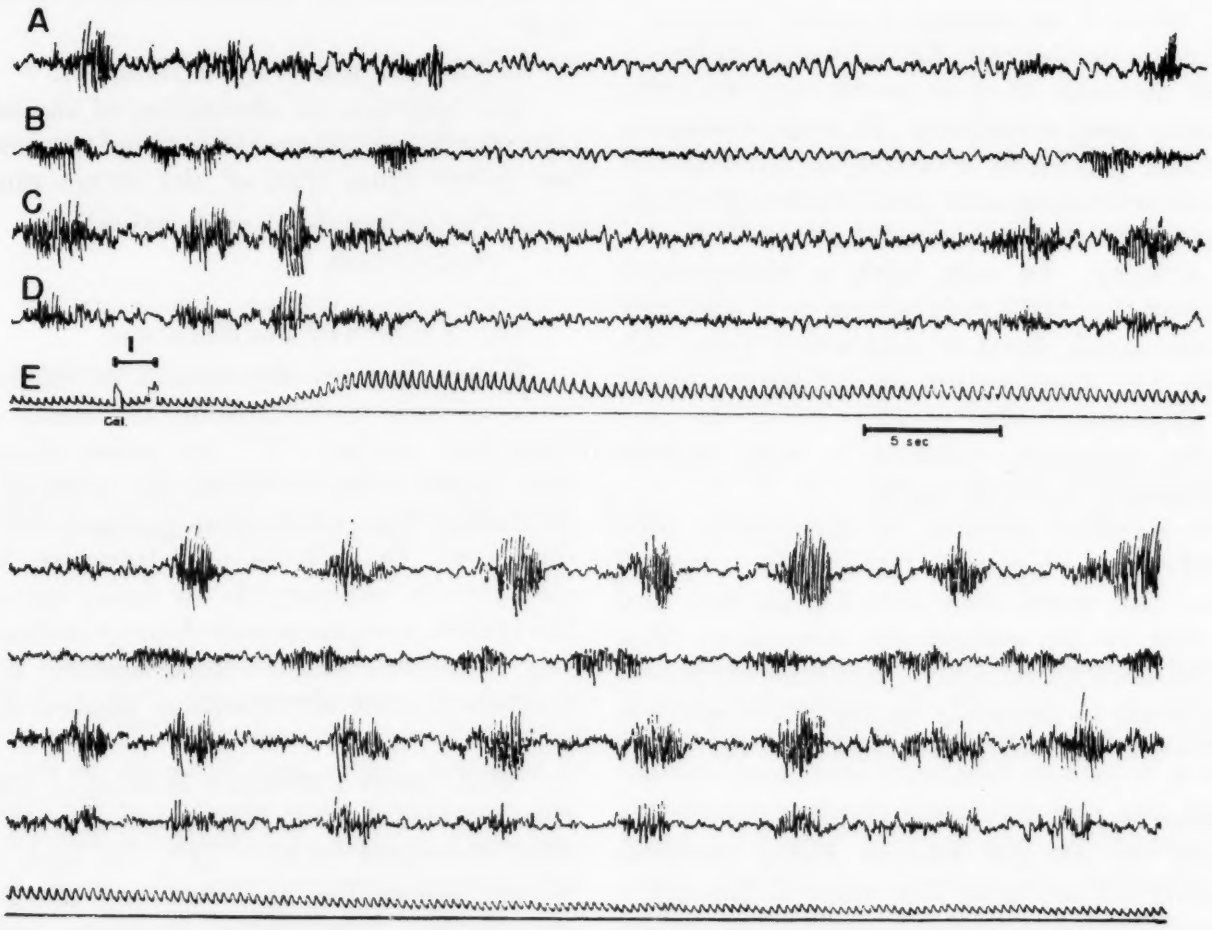


Fig. 6

Effect of the intravenous injection ("I") of 5 μg/kg. of adrenaline upon the EEG of a cat with mid-reticular coagulation. Only the activation phase is seen and it lasts from 10-32 sec. after the beginning of the injection. The EEG activation consists of a shift from pattern "D" to "B". The pressor response is similar to that seen in figure 4.

very little; this was true until the threshold was approached, when the time of onset suddenly shifted and occurred later.

The above protocol also illustrates several other characteristics of the adrenaline response of the cat with mid-reticular coagulation. The threshold for adrenaline was often surprisingly low (in this instance, 0.05 μg/kg.) and EEG activation still occurred with doses of adrenaline too small to produce any rise in the blood pressure, when activation often preceded a *fall* in B.P. The threshold illustrated above was the lowest observed, but thresholds for similar preparations of 1 μg/kg. or less were not unusual. It appears then that the sensitivity to adrenaline of the animal with the brain lesion can be greater than that of the intact cat. Part of this may be due to the greater ease of detecting a response against a deactivated EEG background.

(*c*) *Intensity of Response*

Although the usual effect of adrenaline is to convert the EEG pattern from "D" to "B", occasionally, it is converted to "A", the degree of activation (in frequency and amplitude) quite comparable to that observed immediately after a painful stimulus in the intact cat. This is illustrated in figure 7. EEG activation from adrenaline this intense (to pattern "A") has never been seen in the intact animal and has been most frequently observed in cats with rather extensive reticular coagulations. It seems necessary to conclude then that mid-reticular coagulation may either lower the apparent threshold to adrenaline, or increase the intensity of the response, although rarely both in any one cat.

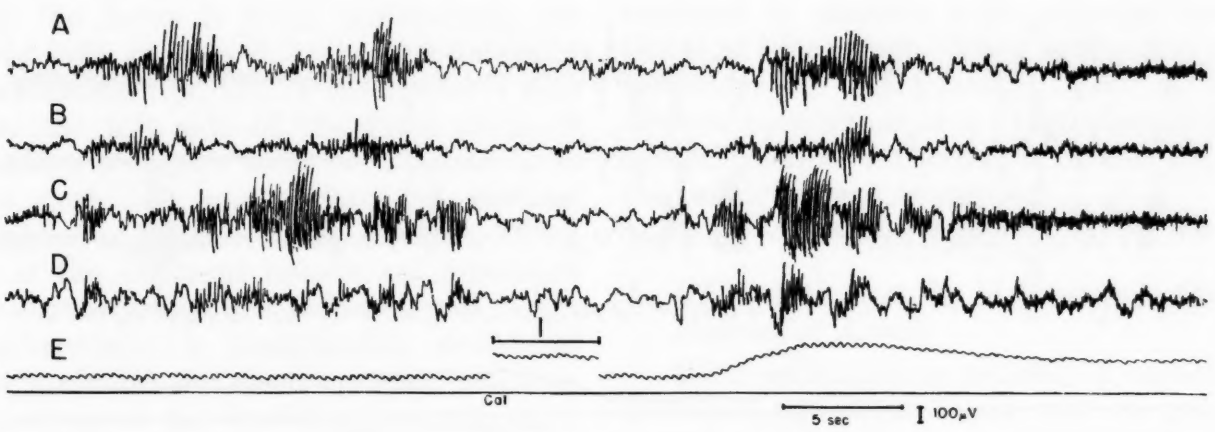
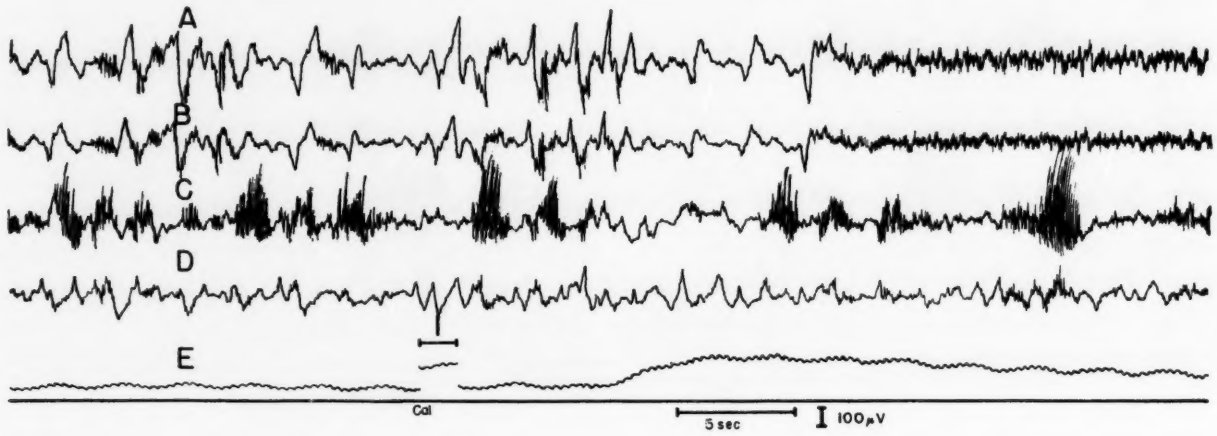


Fig. 7.

Effect of the intravenous injection ("I") of 8 μg/kg. of adrenaline upon the EEG of a cat with mid-reticular coagulation. EEG activation begins about 16 sec. after the beginning of the injection and is very intense, constituting a shift from pattern "D" to "A".

(d) Effect of Further Coagulation of the Mesencephalic Tegmentum upon the Threshold and Pattern of Adrenaline EEG Activation; Unilateral Electrographic Arousal

It was observed that, in general, the more extensive the coagulation of the brain stem necessary to produce the desired EEG background, the higher the threshold to adrenaline. Some hours after the original adrenaline threshold was determined (the noradrenaline threshold having been measured in the meantime), the adrenaline threshold was again determined and found to lie between 0.20 and 0.25 μg., i.e. scarcely different from the original determination. Brain stem coagulation was then performed 3 mm. anterior to the original lesion and on the left side (coordinates F + 3, L2, 6 (left), H—2), and



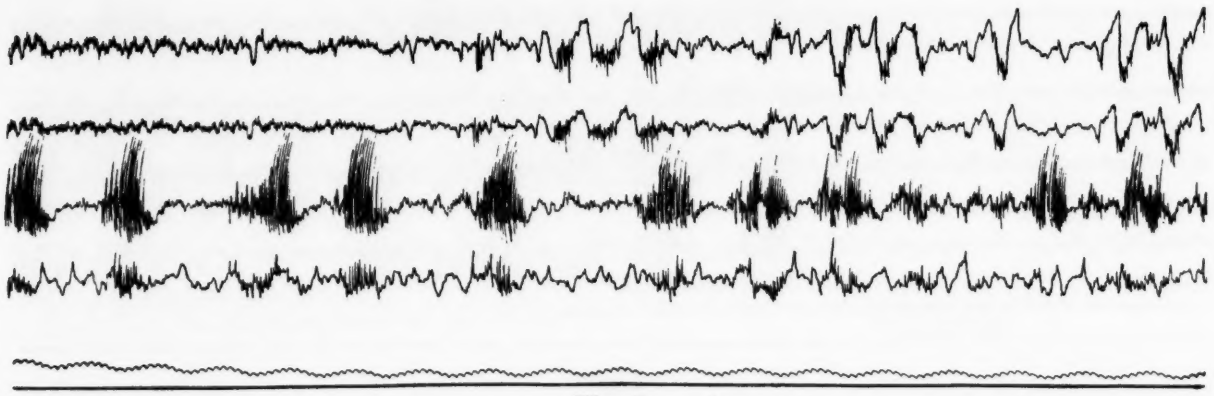


Fig. 8

Effect of the intravenous injection ("I") of 5 μg/kg. of adrenaline upon the EEG of a cat in which coagulation of the left half of the mesencephalic tegmentum had been performed. Intense EEG activation is noted on the EEG recorded from the right cerebral hemisphere (channels A and B) but no change is apparent in the recordings from the left hemisphere (channels C and D).

Since the adrenaline sensitivity even in intact animals is seen to vary somewhat, further evidence was sought on the correlation between the amount of mesencephalic reticular formation left intact and adrenaline sensitivity. This was done by progressively destroying the mesencephalic tegmentum, advancing the coagulating electrodes rostrally in 2 mm. steps, unilaterally or bilaterally. The following is abstracted from the same experiment cited above (RC 28):

the threshold again determined. Five μg. of adrenaline produced only right-sided EEG activation, but 15 μg. produced a bilateral response. Coagulation was repeated (at F + 7, L2, 6 (left) H O), whereupon it was found that 15 μg. of adrenaline produced activation, but on the right side only, and that it was impossible to produce bilateral activation with any reasonable dose. An illustration of this unilateral EEG activation to adrenaline is given in figure 8.

The above data, along with the results from other experiments in which lesions were made in the mesencephalic tegmentum in similar fashion or bilaterally, allow one to conclude that the adrenaline sensitivity of such a preparation is roughly directly proportional to the amount of mesencephalic tegmentum left intact, and that by progressively destroying this region in a rostral direction, the threshold is progressively raised. Furthermore, if the lesion is made unilaterally, the threshold will be raised higher ipsilaterally than contralaterally, i.e., if the lesion is confined to the left side of the brain stem, it will require a higher dose of adrenaline to produce both left and right-sided cortical activation than right-sided activation alone. Lastly, if the bilateral lesions are advanced sufficiently rostrally, the response will disappear altogether; a comparable *unilateral* lesion will abolish the electrographic response to adrenaline of the *ipsilateral* cortex only, although it will raise the threshold of the contralateral cortical EEG response somewhat.

F. *Effects of Noradrenaline Administration*

Early in the course of these experiments it was observed that noradrenaline had an EEG activating effect indistinguishable from that of adrenaline. Subsequently attempts were made to measure the adrenaline and noradrenaline threshold in the same preparation in order to compare the two substances quantitatively. Within the limits of error of the method (probably no greater than 50 per cent) it is possible to state that equal weights of the two substances have approximately equal effects upon the EEG. Furthermore by using the two drugs alternately and gradually reducing the dose towards the threshold level the minimum effective dose capable of producing EEG activation was also found to be the same for the two drugs.

The effect upon blood pressure was of course not the same. The pressor effects of noradrenaline were greater in magnitude and duration than those of equal doses of adrenaline. While the minimum dose of adrenaline producing EEG activation sometimes produced no blood pressure change or a fall, the equivalent dose of noradrenaline always still produced a slight rise.

The effects of noradrenaline were comparable to those of adrenaline in the intact animal and the preparation with mid-reticular coagulation. Brain-stem lesions which abolished the EEG response to adrenaline either unilaterally or bilaterally abolished the response to noradrenaline likewise. Since most of the experience with noradrenaline has been confined to animals with reticular coagulation and since *quantitative* estimation of the inhibitory or deactivating effect of adrenaline or noradrenaline is unsatisfactory in this preparation, no comparison of this effect of the two drugs was attempted.

DISCUSSION

A. *EEG Activation by Adrenaline; Site and Manner of Action*

EEG activation is not only a concomitant of behavioral arousal but may be produced specifically by electrical stimulation of certain well-circumscribed portions of the central nervous system, in particular the bulbar reticular formation, the pontine and mesencephalic tegmentum, subthalamus and dorsal hypothalamus (Moruzzi and Magoun 1949). It is only natural that attention should be drawn to these regions, collectively called the reticular activating system, as a possible site for adrenaline action. If such should prove to be the case, it would be important to distinguish an action of the drug directly upon this neural substrate from any indirect effect mediated through one or more of the many sensory pathways that are known to play upon it. By progressively sectioning the brain stem in a rostral direction, Bonvallet, Dell and Hiebel (1954) were able to show that adrenaline EEG activation persists until intercollicular section is performed, proving that the medulla and pons were not indispensible for this response, but that some structure at the collicular level was.

We attempted to localize this responsive area as accurately as possible by making restricted lesions in the midbrain and diencephalon, or by injecting very small quantities of adrenaline directly into this same structure (the results of these investigations will be reported subsequently). Coagulation of the

tegmentum at the ponto-mesencephalic junction did not abolish the response to adrenaline; it lowered the threshold if anything. Other animals with similar or larger lesions, whose adrenaline threshold was not necessarily low, nonetheless showed an unusually intense activation from adrenaline (pattern "A"). This seems to correspond to the findings of Bonvallet, Dell, and Hiebel (1954) who noted a particularly marked adrenaline EEG activation after pre-bulbar brain stem section.

Sufficient destruction of the mesencephalic tegmentum in a rostral direction was capable of abolishing the EEG response to adrenaline altogether, showing that the integrity of this region is necessary for the adrenaline action, and demonstrating that adrenaline acts upon it, or at least through it. Partial destruction of this region simply raises the threshold to adrenaline in a manner rather proportional to the extent of the lesion, suggesting that each portion of this region makes a contribution to the total response. Unilateral coagulation of the mesencephalic tegmentum is capable of abolishing the response to adrenaline strictly ipsilaterally, the other hemisphere serving as an excellent control. The system is apparently uncrossed between the midbrain and cortex.

The above evidence shows that the mechanism of adrenaline EEG activation is not to be sought in any diffuse cortical effect, either upon the blood vessels or the nervous elements, but rather is dependent upon a fairly circumscribed portion of the brain stem. The ways in which adrenaline might affect this region will be considered.

Electrographic activation by adrenaline is not the consequence of a rise in blood pressure. The EEG changes sometimes precede by several seconds the pressor response; activation often disappears during the phase of rapid blood pressure increase and returns as the pressure is gradually falling. When using very small doses of adrenaline EEG activation may be accompanied by no discernible alteration in blood pressure or a fall rather than a rise.

The EEG response to adrenaline is unlikely to be due to effects upon cerebral blood vessels or blood flow. Adrenaline and noradrenaline generally have the opposite effect upon blood vessels, the former being predominantly vasodilator, the latter vasoconstrictor (Goldenberg *et al.* 1948); at those sites where their actions are similar (coronary vasodilatation, and skin vasoconstriction), their effects are not quantitatively the same. Adrenaline produces an increase in total cerebral blood flow, whereas noradrenaline causes a decrease (King, Sokoloff, and Wechsler 1952). Despite all these important differences, these two agents have, on a weight basis, indistinguishably similar effects upon the EEG. Moreover very small doses of barbiturates, which have no perceptible effect upon the vascular responses, block EEG activation altogether (Bonvallet, Dell and Hiebel 1954). Although a restricted local vascular action cannot be ruled out until it is possible to study the effects of all these drugs specifically upon brain stem blood flow, such a mechanism does not at present account satisfactorily for the central effects of adrenaline.

The stimulating effect which adrenaline has upon the metabolism of tissues in general and upon cerebral oxygen consumption in particular also fails to account for the EEG activation, for while noradrenaline is just as effective as adrenaline in producing EEG activation, it is much less active metabolically (Reale *et al.* 1950; King *et al.* 1952).

It can be argued that adrenaline might produce some peripheral sensation which, firing into the reticular formation, would in turn arouse the animal. However, the preparation with mid-reticular coagulation is less responsive to ordinary stimuli such as light, touch, or sound, and much less sensitive to pain than the intact cat. Nevertheless, such preparations are often more sensitive than the intact cat to the EEG effects of adrenaline. Moreover, Bonvallet, Dell and Hiebel (1954) have demonstrated EEG activation from adrenaline in the "cerveau isolé" preparation.

By its action, adrenaline sets in motion a number of reflex readjustments, principal among which is stimulation of the carotid and aortic pressoreceptors. However the effect upon the EEG of stimulating these receptors has been shown to be inhibitory, i.e., deactiva-

tion (Bonvallet, Dell, and Hiebel 1954), thus scarcely accounting for adrenaline's predominantly activating effect.

There is every reason to believe then that adrenaline exerts its effects directly upon the neural elements themselves, rather than indirectly through vascular, reflex, or sensory mechanisms. Furthermore, the only neurones which appear indispensable are those located primarily in the mesencephalic tegmentum, a region where electrical stimulation will produce precisely the same effect, EEG activation. All the evidence suggests that noradrenaline acts in the same manner and is about equally effective.

B. *Participation of the Adrenal Glands; Delayed Arousal*

Bonvallet, Dell and Hiebel (1954) have shown quite clearly that EEG activation may result not only from injections of adrenaline but also from endogenous adrenaline released by splanchnic nerve stimulation. Furthermore they have shown a late phase of EEG activation which appears following sciatic stimulation when the immediate activation had been abolished by pre-bulbar section; it has about the same delay (10-15 sec.) as that following adrenaline injection or splanchnic stimulation. Since sciatic stimulation is known to produce discharge of adrenal medullary hormones (principally adrenaline rather than noradrenaline, von Euler and Folkow 1953) it is likely that this late phase is due to endogenous adrenaline release. A similar pattern has been seen after brain stem coagulation (fig. 3) when the immediate response to sciatic stimulation has been sufficiently reduced to allow the late phase to stand out clearly (compare with fig. 4). It is not seen more often after mid-reticular coagulation most probably because the lesion frequently involves the rostral pons where the adrenaline-release reflex center has been localized by Cannon and Rapport (1921); thus after mid-reticular coagulation both the pressor and adrenaline-release reflex responses to sciatic stimulation are often absent.

An attempt was made to assess the contribution of the adrenals to the EEG response which follows sciatic stimulation by studying the same response in adrenalectomized animals (two intact and one with mid-reticular coagulation). After sciatic stimulation EEG activation occurred promptly and lasted as it did in their non-adrenalectomized counterparts (0-60 sec.); EEG activation to injected adrenaline occurred as in the non-adrenalectomized animals (10-40 sec.). It is apparent that the purely neural phase of EEG activation completely overlaps and may outlast the "humoral" phase due to adrenaline, this accounting for the fact that two distinct phases of EEG activation or increase in blood pressure are so rarely seen in the intact animal. The contribution of the adrenal glands to EEG activation after a brief noxious stimulus is small and ordinarily obscured by the neural phase, but it does appear as a separate phase under certain experimental conditions in which case it is important to recognize it. There is nothing to suggest from observations of adrenalectomized animals or man that the adrenal medulla plays any role in maintaining alert wakefulness.

It must be mentioned, however, that not all delayed EEG activation is necessarily due to a humoral mechanism involving the blood stream or adrenal glands. A 2-3 sec. delay in EEG activation after a noxious stimulus was observed by Lindsley *et al.* (1950) in chronic cats with lesions of the direct sensory pathways. A delay as long as 30 sec. between a very mild tactile stimulus and EEG activation has been observed repeatedly in a cat with peripherally placed mesencephalic lesions (Sharpless and Rothballer 1955) and in intact monkeys (Morrell 1955). A similar sort of delay is observed to follow gentle rousing of someone deeply asleep.

The adrenal glands were not responsible for the delayed response because in the first instance (Lindsley *et al.* 1950) the interval was too short (less than the minimum latent period ever observed between injection of adrenaline directly into the inferior vena cava and subsequent EEG activation); in the second instance (Sharpless and Rothballer 1955), the delayed response persisted after bilateral adrenalectomy; in the last instance (Morrell 1955), the stimuli were mild and quite unlike those strong enough to induce sympatho-adrenal discharge. It should be recognized then that EEG activation may ap-

pear after an appreciable latent period following the initiating stimulus. This is most likely to appear when the stimulus is very mild or after *peripherally-placed* mesencephalic lesions (involving direct sensory pathways); it is unrelated to adrenal medullary discharge.

The reverse situation is seen after *centrally-placed* mesencephalic lesions, in which case the EEG activation following a noxious stimulus is immediate but does not outlast the stimulus. This has been observed by Lindsley *et al.* (1950) in chronic preparations, and we have made the same observation in some of our animals with mid-reticular coagulation. Taken together, the evidence suggests that peripherally-placed mesencephalic pathways mediate a very prompt EEG activation in response to noxious stimuli which is poorly sustained when working alone. On the other hand, centrally-located mesencephalic structures mediate a sustained EEG activation effect which is apt to show a long latent period when acting alone or when the stimulus is very mild.

C. *The Adrenergic Component of the Reticular Activating System*

It might be asked why any circumscribed portion of the brain should show such marked and specific sensitivity to adrenaline and noradrenaline. Of probable pertinence to the question is the observation that this same region contains both these substances (7 per cent adrenaline and 93 per cent noradrenaline in the cat); the content of these substances is labile and falls after noxious stimuli such as anoxia or ether anaesthesia, and it has been suggested that they participate actively in the function of these regions (Vogt 1954).

All of the above mentioned facts plus additional observations that will be presented subsequently in connection with adrenergic sensitizing and blocking agents have suggested the possibility that at least some of the reticular activating system is actually adrenergic, i.e., that adrenergic substances (probably principally noradrenaline) participate in synaptic transmission. Since there are reasons to believe that the reticular activating system is not entirely homogeneous functionally or neurohumorally, such a system will be referred to tentatively as the *adrenergic component* of the reticular activating system. A similar proposal has been made by Dell, Bonvallet, and Hugelin (1954) in the discussion of their observations on the adrenaline-sensitivity of the descending bulbar fascilitatory system.

Up to the present time, studies of synapses have been made on those which are presumably cholinergic. Compared to acetylcholine, however, adrenergic transmitter substances occurring peripherally (principally noradrenaline) are destroyed much more slowly; excitation of the peripheral sympathetic system produces effects which are generalized, sustained and which fluctuate comparatively slowly, over seconds or minutes, rather than milliseconds. Such properties as these are not dissimilar to those just attributed to the centrally-placed EEG activating mechanisms — those which produced EEG activation of a sustained sort well outlasting the stimulus, but which as mentioned may show a certain amount of delay. It is suggested then that the mechanism subserving sustained EEG activation, and its behavioral counterpart, consciousness or wakefulness, is at least partly the adrenergic component of the reticular activating system. The properties of such a system may account for some of the characteristics of the conscious state, including its prolonged, tonic nature, the slowness with which changes in it normally take place and possibly the long latent period between a gentle stimulus and complete arousal from deep sleep.

D. *Adrenaline EEG Deactivation*

It has been stressed that although EEG activation is the most prominent effect of adrenaline, it also has the opposite effect, deactivation. The first phase of deactivation usually occurs just as the blood pressure starts to rise and is rather brief. The second phase comes later as the blood pressure is falling or has returned to normal, when phases of activation and deactivation sometimes alternate with one another. Although only activation from adrenaline was mentioned by Bonvallet, Dell, and Hiebel (1954), their record of adrenaline EEG action (fig.

8, page 127) also shows this early deactivation phase quite clearly. Thus there is reason to conclude that the duration of EEG activation does not correspond simply with the presence of adrenaline in the brain but is the resultant of two simultaneous and opposing actions, activation and deactivation. At the peak of action of the drug, activation usually predominates, but when levels are rising or falling the phases alternate or deactivation predominates. After preparation of the animal with thiopental, the activation phase is permanently blocked, but the deactivation phase often appears alone.

The deactivation phase may be at least partly due to stimulation of the pressor receptors by the blood pressure rise and consequent inhibition via the bulb (Bonvallet, Dell and Hiebel 1954). This may explain why the animal with mid-reticular coagulation or pre-bulbar section is so unusually sensitive to adrenaline, or responds at times with such an intense activation, but it does not account for the late phase when the blood pressure has often fallen to normal. Adrenaline does seem to have intrinsic inhibitory properties, however. Electrical changes interpreted as showing inhibition of cortical synapses have been reported after intracarotid adrenaline by Marazzi and King (1950). Intravenous adrenaline tends to inhibit the release of vasopressin by the supraoptico-hypophysial system in response to noxious stimuli (O'Connor and Verney 1945), while acetylcholine stimulates this same system (Pickford 1947). Intraventricular injection of adrenaline or noradrenaline in cats produces a state resembling light anaesthesia (Feldberg and Sherwood 1954). Lastly, it is a common pharmacological observation that a drug may stimulate or depress depending on concentration. It seems clear then that there are both excitatory and inhibitory elements to the central effects of adrenaline (much as there are to its peripheral effects) and that in the final analysis its influence upon the EEG is the resultant of these two opposing actions.

B. *Cholinergic EEG Activation*

The conclusion has been drawn that the reticular activating system is cholinergic, on the basis of experiments which have demonstrated EEG activation in the curarized rabbit from intracarotid acetylcholine or cholinergic potentiators such as DFP, and its abolition with atropine (Rinaldi and Himwich 1955 a and b). Others have made similar observations (Bradley 1953; Longo 1955). Working with freely moving intact cats from which EEG records were made simultaneously, Bradley (1953) has made important observations on the correlation between EEG activity and behavior. In such preparations, amphetamine produced both EEG and behavioral arousal, while physostigmine produced EEG "arousal" with no concomitant behavioral change. This important dissociation between the EEG and behavior was first noted by Wikler (1952) in atropinized dogs, which showed EEG sleep patterns when they were awake or even excited. This was confirmed in the cat (Bradley 1953) and we have observed it ourselves. Furthermore, Bradley (1953) noted that mesencephalic transection abolished the EEG effectiveness of amphetamine but did not eliminate the EEG activating effects of physostigmine, suggesting a different site of action. Rinaldi and Himwich (1955 b) found that the EEG effects of acetylcholine were not abolished by lower mesencephalic transection but were absent in the isolated hemisphere.

All of this evidence suggests certain fundamental differences between the adrenergic and the cholinergic EEG activating mechanisms. The former is closely associated with the mesencephalic reticular formation while the latter may be somewhat more rostrally situated (between the mesencephalon and the centrum ovale). The EEG effects produced by adrenergic sensitizing and blocking agents (amphetamine, chlorpromazine) run parallel to behavior. On the other hand cholinergic potentiating and blocking agents (physostigmine, atropine) produce EEG effects with the conspicuous absence of any behavioral counterpart, i.e., dissociation. At present, the most that one can say is that it appears that the reticular activating system (in its EEG sense only) contains both adrenergic and cholinergic components; the brain stem arousal mechanism (in its behavioral sense) appears to be adrenergic; it re-

mains to be shown that it is cholinergic as well.

SUMMARY AND CONCLUSIONS

Experiments were carried out to determine the effect of adrenaline and noradrenaline upon the EEG of the intact unanaesthetized cat, the adrenalectomized cat and the cat prepared with a lesion of the tegmentum at the ponto-mesencephalic junction (mid-reticular coagulation).

Adrenaline in doses of 2-8 μg/kg. produced a series of alternating phases of EEG activation and deactivation in the period between 6-60 sec. after the beginning of the intravenous injection. Of these, the phase of activation was the most conspicuous, and dominated the middle portion of the response. The deactivation phases came at the beginning and end of the response, and whether or not they were detectable depended primarily upon the background activity.

By coagulating the ponto-mesencephalic tegmentum an apparent increase in sensitivity to adrenaline could be produced, with thresholds encountered as low as 0.05 μg/kg. Reducing the adrenaline dose towards threshold produced a gradual shortening of the activation phase, then a delay in its onset just before the response disappeared altogether. Further coagulation in this same region gradually raised the threshold as the lesions were made more and more anteriorly, although the intensity of the activation response was sometimes actually increased. By carrying the coagulation up to the mesodiencephalic border the response to intravenous adrenaline was abolished altogether. Unilateral mesencephalic coagulation abolished the response only over the ipsilateral hemisphere.

The EEG effects of noradrenaline were qualitatively similar to adrenaline in all respects and equal doses produced responses of approximately the same magnitude.

The responses to adrenaline of the adrenalectomized, cortisone-maintained cat are the same as those of the intact cat. Biphasic or late EEG activation from sciatic stimulation was never observed in this preparation however. The contribution to EEG activation of endogenous adrenaline release is assessed.

Evidence in favor of the existence of an adrenergic component within the reticular activating system is given and some of the possible properties of such a system are discussed.

The supervision, advice and criticism of Dr. H. H. Jasper are gratefully acknowledged, as are the contributions of Dr. Robert Naquet, who participated in many of the foregoing experiments.

REFERENCES

BONVALLET, M., DELL, P. et HIEBEL, G. Tonus sympathique et activité électrique corticale. *EEG Clin. Neurophysiol.*, **1954**, *6*: 119-144.

BRADLEY, P. B. The effect of some drugs on the electrical activity of the brain in the cat. *EEG Clin. Neurophysiol.*, **1953**, *5*: 471.

CANNON, W. B. and RAPPORT, D. Studies on the conditions of activity in endocrine glands. VII. The reflex center for adrenal secretion and its response to excitatory and inhibitory influences. *Amer. J. Physiol.*, **1921**, *58*: 338-352.

CLARK, S. L. and WARD, J. W. Electroencephalogram of different cortical regions of normal and anaesthetized cats. *J. Neurophysiol.*, **1945**, *8*: 99-112.

DELL, P., BONVALLET, M. et HUGELIN, A. Tonus sympathique, adrénaline et contrôle réticulaire de la motricité spinale. *EEG Clin. Neurophysiol.*, **1954**, *6*: 599-618.

VON EULER, U. S. The nature of adrenergic nerve mediators. *Pharmacol. Rev.*, **1951**, *3*: 247-277.

VON EULER, U. S. und FOLKOW, B. Einfluss verschiedener afferenter Nervenreize auf die Zusammensetzung des Nebennierenmarkinkretes bei der Katze. *Arch. exp. Path.*, Berlin, **1953**, *219*: 242-247.

FAURE, J. De quelques actions pharmacologiques sur les potentials électriques de la base du cerveau chez l'homme. *C. R. Soc. Biol.*, **1949**, *143*: 391-392.

FELDBERG, W. and SHERWOOD, S. L. Injections of drugs into the lateral ventricles of the cat. *J. Physiol.*, **1954**, *123*: 148-167.

GIBBS, F. A., GIBBS, E. H. and LENNOX, W. G. Effects on the electroencephalogram of certain drugs which influence nervous activity. *Arch. Int. Med.*, **1937**, *60*: 154-166.

GIBBS, F. A. and MALTBY, G. L. Effect on the electrical activity of the cortex of certain depressant and stimulant drugs — barbiturates, morphine, caffeine, benzedrine, and adrenalin. *J. Pharmacol. Exper. Therap.*, **1943**, *78*: 1-10.

GOLDENBERG, M., PINES, K. L., BALDWIN, E. de F., GREEN, D. G. and ROTH, C. E. The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. *Amer. J. Med.*, **1948**, *5*: 792-806.

GOTTSCHALK, L. A. Effect of epinephrine on cortical and basal electroencephalograms and the eosinophil count. *Arch. Neurol. Psychiat.*, Chicago **1952**, *67*: 522-534.

GREEN, J. D. and MORIN, F. Hypothalamic electrical activity and hypothalamo-cortical relationships. *Amer. J. Physiol.*, **1953**, *172*: 175-186.

GREENBLATT, M., FUNKENSTEIN, D., MILLER, D. and RINKEL, M. Electroencephalographic patterns from the base of the brain. *Amer. J. Psychiat.*, **1947**, *103*: 749-757.

GRINKER, R. R. and SEROTA, H. M. Electroencephalographic studies of corticohypothalamic relations in schizophrenia. *Amer. J. Psychiat.*, **1941**, *98*: 385-392.

HESS, R. Jr., KOELLA, W. P. and AKERT, K. Cortical and subcortical recordings in natural and artificially induced sleep in cats. *EEG Clin. Neurophysiol.*, **1953**, *5*: 75-90.

HESS, R. Jr. Bioelectrical and behavioral arousal with electrical stimulation of the meso-diencephalic structures. *EEG Clin. Neurophysiol.*, **1954**, *6*: 528-529.

INGVAR, D. H. Extraneuronal influences upon the electrical activity of the isolated cortex following stimulation of the reticular activating system. *Acta Physiol. Scand.*, **1955**, *33*: 169-193.

JASPER, H. H. and ERICKSON, T. C. Cerebral blood flow and pH in excessive cortical discharge induced by metrazol and electrical stimulation. *J. Neurophysiol.*, **1941**, *4*: 333-347.

KING, B. D., SOKOLOFF, L. and WECHSLER, R. L. The effects of L-epinephrine and L-nor-epinephrine upon cerebral circulation and metabolism in man. *J. Clin. Invest.*, **1952**, *31*: 273-279.

KLÜVER, H. and BARRERA, E. A method for the combined study of cells and fibers in the nervous system. *J. Neuropath. Exper. Neurol.*, **1953**, *12*: 400-403.

LINDSLEY, D. B., SCHREINER, L. H., KNOWLES, W. B. and MAGOUN, H. W. Behavioral and EEG changes following chronic brain stem lesions in the cat. *EEG Clin. Neurophysiol.*, **1950**, *2*: 483-498.

LONGO, V. G. Acetylcholine, cholinergic drugs, and cortical electrical activity. *Experientia*, **1955**, *11*: 76-78.

MAGOUN, H. W. The ascending reticular system and wakefulness. Pages 1-20 in *Brain Mechanisms and Consciousness*. Springfield, Ill., Charles C. Thomas, **1954**.

MARAZZI, A. S. and KING, E. E. Effects of humoral agents on cortical evoked potentials in monosynaptic preparations. *Fed. Proc.*, **1950**, *163*: 732.

MINZ, B. and DOMINO, E. F. Effects of epinephrine and norepinephrine on electrically induced seizures. *J. Pharmacol. Exper. Therap.*, **1953**, *107*: 204-218.

MINZ, B. et RÉMOND, A. Modifications de l'excitabilité corticale du singe sous l'action de l'adrénaline. *EEG Clin. Neurophysiol.*, **1953**, *5*: 132.

MORRELL, F. Personal Communication.

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and the activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

O'CONNOR, W. J. and VERNEY, E. B. The effect of increased activity of the sympathetic system in the inhibition of water diuresis by emotional stress. *Quart. J. Exper. Physiol.*, **1945**, *33*: 77-90.

PICKFORD, M. The action of acetyl choline in the supraoptic nucleus of the chloralosed dog. *J. Physiol.*, **1947**, *106*: 264-270.

PORTER, R. W. Alterations in electrical activity of the hypothalamus induced by stress stimuli. *Amer. J. Physiol.*, **1952**, *169*: 629-637.

REALE, A., KAPPERT, A., SKOGLUND, C. H. and SUTTON, G. C. The effect of L-nor-epinephrine on the oxygen consumption of human beings. *Acta Physiol. Scand.*, **1950**, *20*: 153-159.

RHEINBERGER, M. B. and JASPER, H. H. Electrical activity of the cerebral cortex in the unanaesthetized cat. *Amer. J. Physiol.*, **1937**, *119*: 186-196.

RINALDI, F. and HIMWICH, H. E. Alerting responses and the actions of atropine and cholinergic drugs. *Arch. Neurol. Psychiat.*, Chicago, **1955**a, 73: 387-395.

RINALDI, F. and HIMWICH, H. E. Cholinergic mechanism involved in function of mesodiencephalic activating system. *Arch. Neurol. Psychiat.*, Chicago, **1955**b, *73*: 396-402.

SHARPLESS, S. and ROTHBALLER, A. Unpublished observations.

VOGT, M. The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *J. Physiol.*, **1954**, *123*: 451-481.

WIKLER, A. Pharmacologic dissociation of behavior and EEG "sleep patterns" in dogs: Morphine, N-allylnormorphine, and Atropine. *Proc. Soc. Exper. Biol. Med.*, **1952**, *79*: 261-265.

Montreal Neurological Institute. Reprint No. 537.

Reference: ROTHBALLER, A. B. Studies on the adrenaline-sensitive component of the reticular activating system. *EEG Clin. Neurophysiol.*, **1956**, *8*: 603-621.

ANNOUNCEMENTS

POST DOCTORATE FELLOWSHIPS

The Sister Elizabeth Kenny Foundation announces a program of post doctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of the neuromuscular diseases.

The Kenny Foundation Scholars will be appointed annually. Each grant will provide a stipend for a five year period at the rate of $5,000.00 to $7,000.00 a year depending upon the Scholar's qualifications. Candidates from medical schools in the United States and Canada will be eligible.

Inquiries regarding details of the program should be addressed to : Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, 2400 Foshay Tower, Minneapolis 2, Minnesota.

RESEARCH PRIZE

The Hofheimer Prize of $1,500 is awarded annually by the American Psychiatric Association for an outstanding research contribution in the field of psychiatry or mental hygiene which has been published within three years of the date of the award. The competition is open to citizens of the United States and Canada not over forty years of age at the time the article was submitted for publication ; or to a group whose median ages do not exceed forty years of age. The next award will be made at the Annual Meeting of the Association in May, 1957. Articles submitted to the Prize Board before March 1st, 1957 will be considered. Eight copies of each publication and data concerning age and citizenship should be sent to Theodore Lidz, M.D., Chairman, Hofheimer Prize Board, 333 Cedar Street, New Haven, Connecticut.

ELECTROGRAPHIC ASPECTS OF AN "AROUSAL" OR ATTENTION REACTION INDUCED IN THE UNANESTHETIZED RABBIT BY THE PRESENCE OF A HUMAN BEING

H. GANGLOFF and MARCEL MONNIER

Laboratoire de Neurophysiologie appliquée, Genève, Suisse

(Received for publication: February 3, 1956)

Experiments performed in unanesthetized rabbits with cortical and subcortical recording electrodes in the lateral and medial thalamus, rhinencephalon and reticular formation of the midbrain have given us the opportunity of analyzing some electrographic patterns of the brain under normal conditions. One of the EEG patterns described here has been regularly observed in most of the 200 rabbits examined with the same recording technique. It appeared under various conditions, not only after exteroceptive stimulations (light, noise, touch or nocive stimuli), but in some cases also in response to a change of the surroundings, with more specific significance for the animal, such as the approach of a human being. In fact, the appearance of a human being moving in the surroundings of the animal proved to be a much more effective stimulus than the exteroceptive stimuli mentioned above. Repetition of this physiological stimulation seem to facilitate more and more the occurrence of the complexe electrographic response to be described here — possibly by conditioned mechanisms — so that it finally occurred apparently spontaneously, in the absence of any environmental stimulus.

We present here a typical example of the electrographic alterations induced in the cortical and subcortical structures by attention in the unanesthetized animal.

METHODS

The electrical brain activity was recorded with a stereotaxic technique previously described by Gangloff and Monnier (1955). A socklet, screwed on the skull under local anesthesia, was used to fix epidural silver electrodes over the sensorimotor and occipital cortex. This also allowed the introduction of silver electrodes, insulated except at the tip, into the medial and lateral thalamus, the rhinencephalon and the reticular formation of the midbrain (fig. 1). The holes were bored in the skull one day before the experiment and the skin sutured again in order to allow the animal to recover in a moderately heated and quiet hutch, with no other contact than that of the operator performing the experiment. During this experiment the animal was kept in a shielded room, separated by an opened door from the adjacent recording room.

The electrical activity was amplified and recorded with a Schwarzer 8-channel electroencephalograph. The respiration was registered by means of a thermocouple fixed in a mask before the nostrils of the animal. The examination lasted 1½ hours and ended about 80 min. after the first stimulation.

RESULTS

During the first 25 min. of the experiment, no definite EEG changes could be observed after visual and auditory stimuli. The EEG pattern showed in the cortical and subcortical leads a continuous, irregular, high voltage, slow wave activity, except in the midbrain reticular formation. Occasionally spindles appeared in the sensorimotor cortex of both hemispheres. The thalamic and rhinencephalic basic rhythm consisted of a more or less irregular 4-5 c/sec. rhythm. Low voltage fast components were seen also in the rhinencephalon and in the lateral thalamus, as well as in the midbrain reticular formation. The EEG was free from any spontaneous alterations. The heart and respiratory rates were regular (fig. 2 A, B). However, every time the operator entered the shielded room in which the animal was isolated, or became visible through the door, the EEG immediately showed the following typical changes:

(1) Suppression of the cortical slow waves and spindles with substitution of low voltage

fast waves in the whole cortex, but chiefly in the sensorimotor areas of both hemispheres. This desynchronization reaction was followed by reappearance of the irregular slow wave activity and of the spindles (fig. 2 C).

(2) Increase in regularity, frequency and some predominance and greater constancy in the occipital cortex (fig. 2 and 3).

(3) Suppression of the rhinencephalic irregular slow wave activity, replaced by a faster, more regular rhythmic activity synchronized with the thalamic 5-7 c/sec. rhythm;

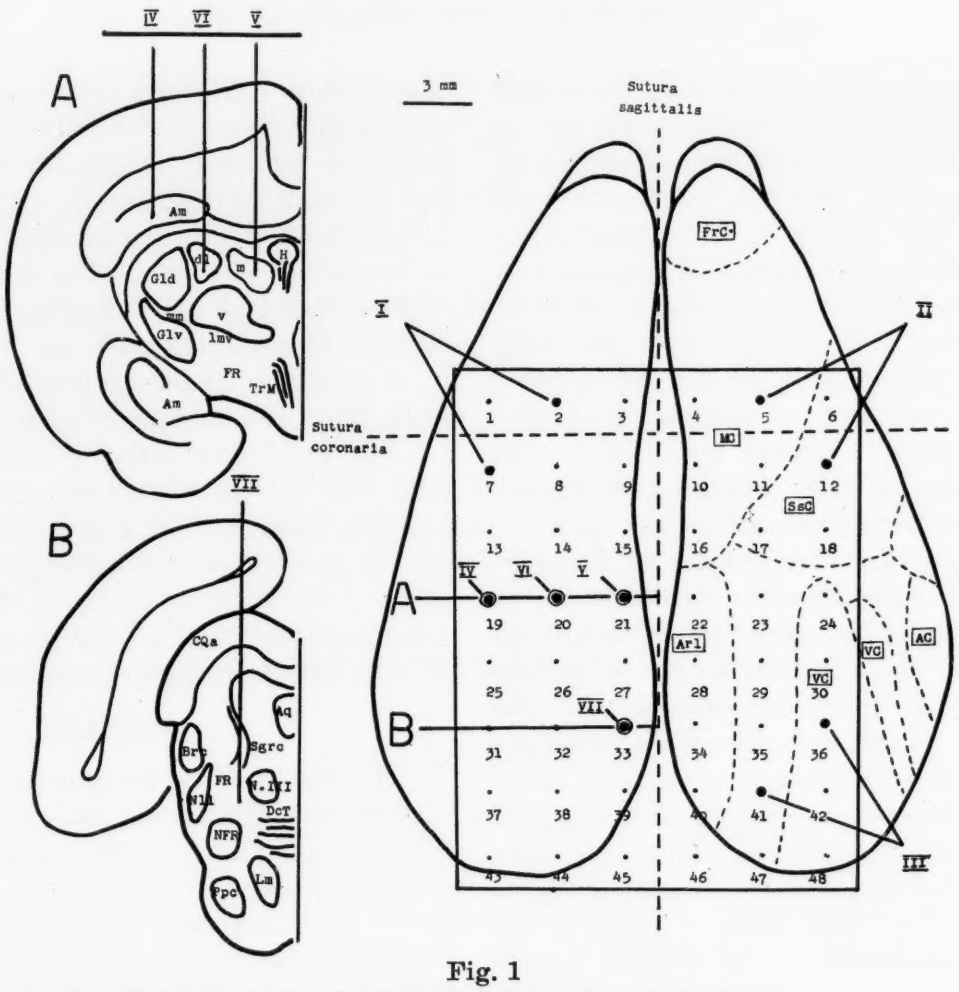


Fig. 1

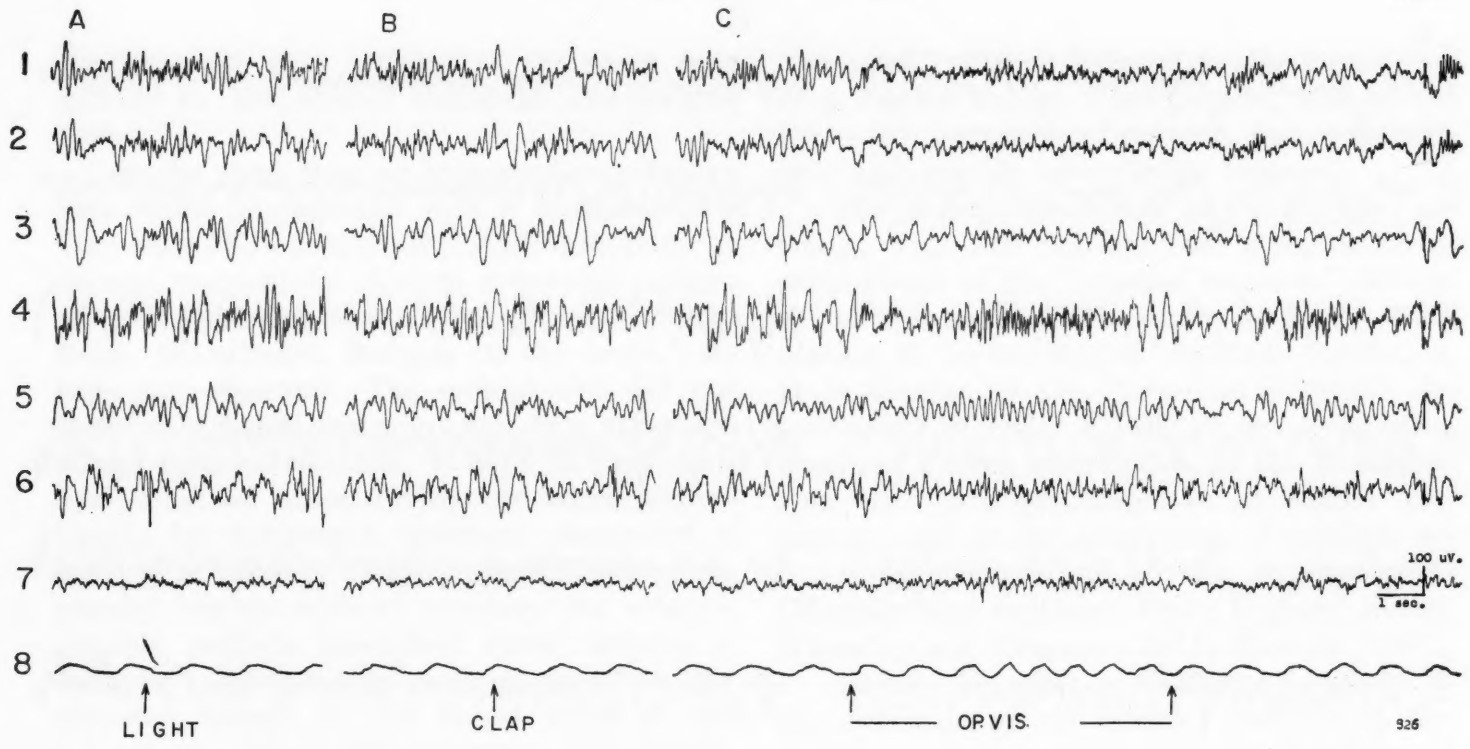
Location of the cortical and subcortical derivation electrodes.

A. Cortex: FrC = frontal cortex; MC = motor cortex; SsC = sensory cortex; VC = visual cortex; AC = auditory cortex; Arl = area limbica (after Rose and Kornmüller).

B. Subcortex: Am = cornu ammonis (Rhinencephalon); Gld = Ggl. genic. dors.; Glv = Ggl. genic. ventr.; mm = lamina med. med.; lmv = lamina med. ventr.; dl = Nucl. dors. lat. thalami; m = Nucl. med. thalami; v = Nucl. ventr. thalami; H = Nucl. habenulae; TrM = Tractus Meynert; Fr = formatio reticularis; CQa = Corp. quadrig. ant.; Aq = Aquaeductus Sylvii; Sgrc = Subst. grisea centr.; DcT = Decussatio tegmenti; Brc = Brach. conjunctivum; Nll = Nucl. lemnisci lat.; NFR = Nucl. form. reticul.; Lm = Lemniscus med.; Ppc = Pes pedunculi; N.III = Nucl. N. oculomot.

voltage of the thalamic rhythmic activity (5-7 c/sec. instead of 4-5 c/sec.), slightly more pronounced in the medial than in the lateral thalamus. Tendency to generalization of this 5-7 thalamic rhythm all over the brain, with increase in voltage of the rhinencephalic fast components (fig. 2 and 3).

(4) Occasionally, slight increase in voltage of the fast wave ground activity in the reticular formation of the midbrain, simulta-



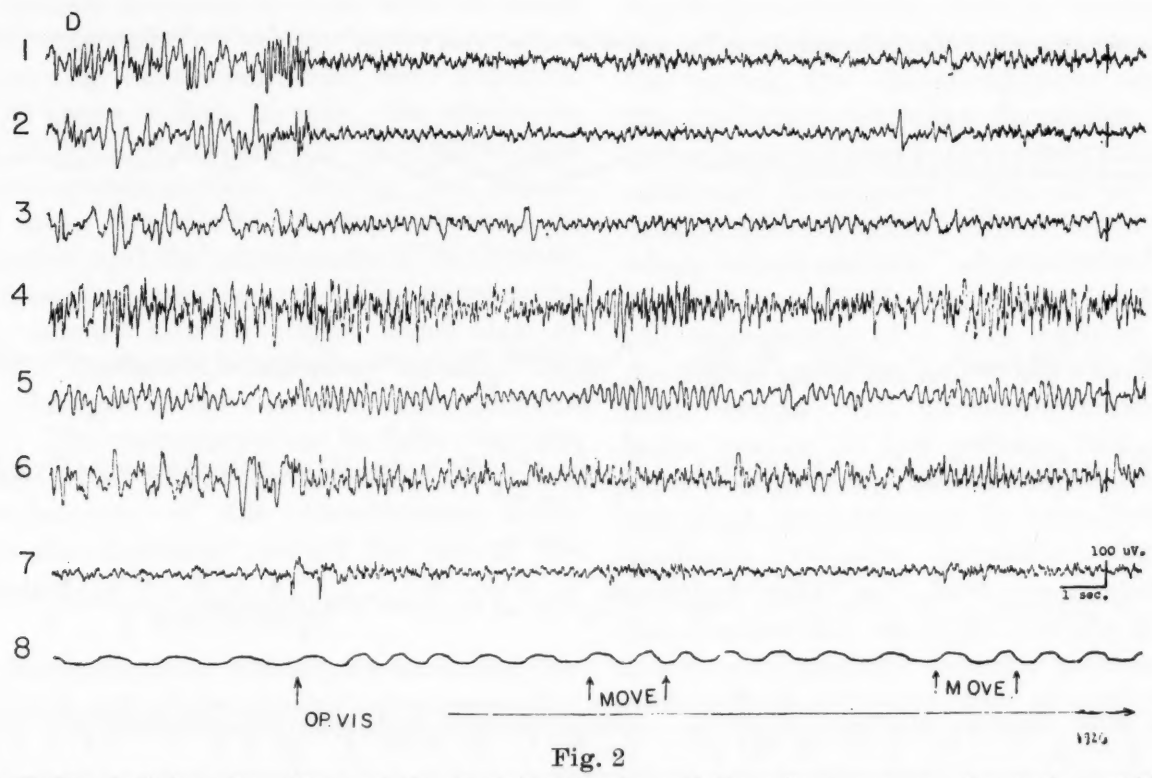


Fig. 2

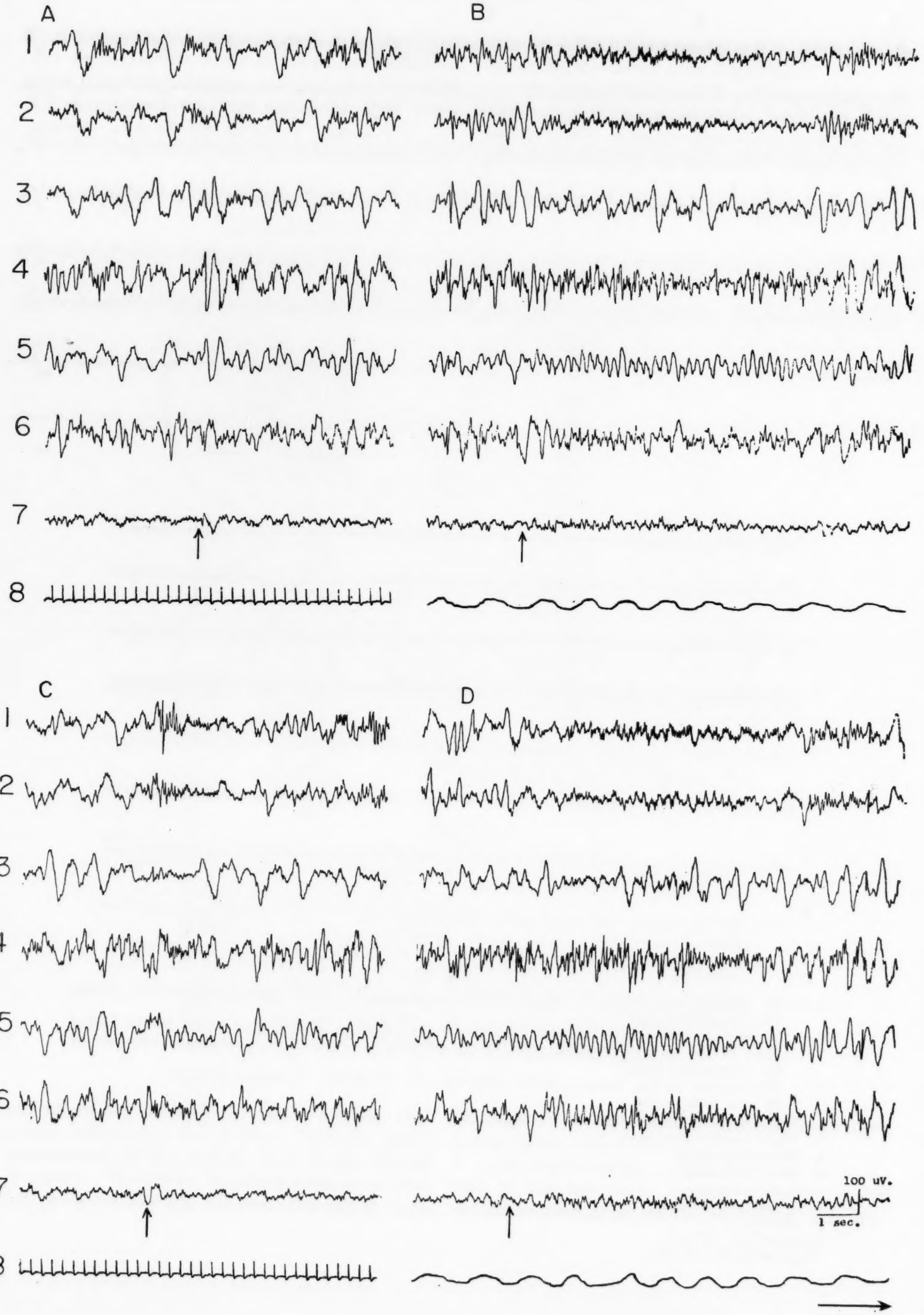
A, B. No definite alterations of the electrical brain activity after sensory stimulation (Light (A), hand clap (B)).

C. Arousal or attentional reaction induced by the presence of a human being in the visual field of the animal (operator visible = OP. VIS.). Note the simultaneous increase of the respiratory rate.

D. Movements of the human being reinforce the electrical ''arousal pattern''.

1. Left sens. mot. cortex
2. Right sens. mot. cortex
3. Right occipit. cortex
4. Rhinencephalon
5. Med. thalamus
6. Lat. thalamus
7. Subst. retic. bulb.
8. E.P.G.

Calibration: 100 μV.
Time-indicator: 1 sec.


A
B
C
D
1
2
3
4
5
6
7
8
100 uv.
1 sec.

neously with fast activity of the same type mainly in the lateral thalamus and in the cortex.

At the same time an increased respiratory rate could be observed with a maximum 3-5 sec. after the onset of the EEG reaction. A normal respiratory rhythm generally returned before the end of the electrographic alterations. Significant changes in the heart rate were not observed. The animal also did not show any motor reaction, nor any other external signs of emotion. It kept its eyes open and remained quiet during the whole experiment; its behaviour, however, suggested a state of attention. If the human observer remained visible without moving, the electrographic pattern described above showed a tendency to decrease, but as soon as the operator moved in the visual field of the animal, the same electrographic and respiratory changes reappeared even with increased intensity (fig. 2 D).

After this experiment had been repeated about 10 times within 15 min., the above described EEG and respiratory alterations also appeared spontaneously. During the following 80 min., the electrical responsiveness to the presence and the movements of the human being remained unchanged. The responsiveness to sensory stimuli (light, hand clap or shouting) increased, inducing similar but shorter changes in the electrographic pattern (fig. 3). The responsiveness to light was less developed than the responsiveness to noise. The occurrence of the spontaneous EEG changes also increased toward the end of the experiment.

DISCUSSION

In unanesthetized rabbits, we have had the opportunity of observing an electrographic "arousal" pattern induced by the perception of a human being. This pattern, also called by us the "attention" pattern, has characteristic and readily identifiable features.

The *desynchronization* of the cortical activity, with low voltage fast components is reminiscent of the "arousal reaction" obtained by Moruzzi and Magoun (1949) by stimulation of the brain-stem reticular formation. It is similar to the "réaction d'éveil" described by Monnier (1950) in the unanesthetized cat during stimulation of the diencephalon with stronger impulses of higher frequency, and to the alterations of cortical activity by stimulation of the hypothalamus (Murphy and Gellhorn 1945; Ingram, Knott, Wheatley and Summers 1951; Hess Jr. 1954).

Among the other mechanisms involved in the evocation of the arousal reaction in the rabbit, we must emphasize acceleration of the thalamic activity with its tendency to synchronize at the same frequency the activity of the cortex, the rhinencephalon and even of the midbrain reticular formation. This observation confirms recent observations of Rinaldi and Himwhich (1955) in the curarized, unanesthetized rabbit. These authors described an "alert pattern" characterized by: "(*a*) elimination of all slow waves and spindles; (*b*) appearance of a very regular 4-7 c/sec. rhythm of medium amplitude, clearly of thalamic origin; (*c*) presence, mainly in the motor cortex, of low voltage fast rhythms." They found that the strongest response of this kind was obtained by stimulation of the midbrain reticular formation. These facts, together with our own observations, prove that the arousal reaction consists not only of a desynchronization pattern with cortical low voltage fast activities, but also of a synchro-

Fig. 3

Increasing responsiveness of the arousal mechanisms to sensory stimulation toward the middle and the end of the experiment.

A. After 25 min. — Light on ↑
B. After 70 min. — Light on ↑
C. After 25 min. — Clap ↑
D. After 70 min. — Clap ↑
1. Left sens. mot. cortex
2. Right sens. mot. cortex
3. Right occipit. cortex
4. Rhinencephalon
5. Med. thalamus
6. Lat. thalamus
7. Subst. retic. bulb.
8. EKG (A,C), E.P.G. (B,D).

Calibration: 100 μV.
Time-indicator: 1 sec.

nization with regular and accelerated 5-7 c/sec. rhythms in the thalamus and in most other subcortical structures. The recent observation of Liberson and Akert (1955) that the presence of an observer leads to a desynchronization of the cortex and to an increased regularity of the rhinencephalic rhythms in unanesthetized guinea pigs belongs to the same group of facts. We can confirm that the rhinencephalic slow activity shows a tendency to increased frequency and regularity and that its fast activities increase in voltage. This is another component of the arousal reaction, which needs further consideration.

These various observations suggest that the arousal mechanisms do not involve the brain stem reticular formation only, but a whole system of cortical and subcortical structures, as already stated by Magoun (1950), Jasper and Ajmone-Marsan (1950) and others. From our own observations we may conclude that three mechanisms at least, showing specific electrographic features, are involved in the arousal system:

(*a*) a *desynchronizing* reticular mechanism producing low voltage fast waves in the reticular formation of the brain-stem itself and chiefly in the cortex;

(*b*) a thalamo-cortical *synchronizing* mechanism showing an acceleration and an increase in regularity of the thalamic basic activity (5-7 c/sec. instead of 4-5 c/sec.), with a tendency to extension to other brain structures.

(*c*) a rhinencephalic mechanism showing a high voltage fast activity and an acceleration of the slower rhinencephalic ground activity (5-7 instead of 4-5 c/sec.) synchronized with the thalamic rhythm.

The most interesting point of our observations is, however, the fact that the mere visual perception of a human being may be a stronger stimulus than other sensory stimuli and may evoke an electrical arousal pattern, whereas neutral visual or auditory stimuli do not disturb the brain activity, as we noted during the first part of the experiment. This facilitatory function of a more elaborate, cortical process — such as the visual perception of an "unpleasant" moving human presence, a process which involves increased attention and possibly even some emotional component — is specially noticeable. Together with the wide-spread electrographic changes accompanying the so-called "arousal" or attention reaction we described, it suggests that the arousal mechanism can be elicited not only from the reticular system in the lower brainstem, or by sensory afferents running into this system, but also from higher cortico-diencephalic and rhinencephalic structures concerned with the regulation of attention and emotional functions. This conclusion is also supported by the observation that the attention pattern described may appear spontaneously without relation to any detectable external stimuli and that it occurs more and more frequently towards the end of the experiment, suggesting that conditioning mechanisms may play a role in its evocation. From a practical point of view, the usefulness of the electrographic techniques described above for experimental psychology is obvious.

SUMMARY

An EEG response recorded simultaneously in the cortex, the medial and lateral thalamus, the rhinencephalon and the midbrain reticular formation of unanesthetized rabbits is described. It consists of: (*a*) suppression of slow waves and bursts in the cortex, and ap pearance of a low voltage fast activity predominant in the sensorimotor areas; (*b*) slight increase in frequency and regularity (5-7 c/sec. instead of 4-5 c/sec.) of the thalamic basic activity, with a tendency to generalization all over the brain, especially in the occipital cortex; (*c*) slight increase in frequency and regularity of the slow rhinencephalic rhythms (5-7 instead of 4-5 c/sec.) synchronized with the thalamic basic activity, and increase in voltage of the rhinencephalic fast components; (*d*) slight increase in voltage of the low voltage fast activities in the midbrain reticular formation appearing simultaneously with the cortical desynchronization. The electrical pattern of this response appears identical with the "arousal" reaction induced by stimulation of the brain-stem reticular formation.

Electrographic evidence is given that the so-called "arousal" system involves at least three mechanism: (1) a reticulo-cortical *desynchronizing* mechanism; (2) a thalamo-cortical *synchronizing* mechanism, leading to

an acceleration and an increase in regularity of the thalamic rhythmic activity, with extension of this rhythm (5-7 c/sec.) all over the brain, even to the midbrain reticular formation; (3) a rhinencephalic mechanism showing high voltage fast activity and an acceleration of the slower rhinencephalic rhythmic activity (5-7 instead of 4-5 c/sec.), synchronized with the thalamic rhythm.

These wide-spread electrographic changes and the responsiveness of the so-called "arousal" system to more elaborate, cortical processes, involving increased attention and possibly some emotional components (visual perception of a moving being) suggest that this system may be activated by sensory afferents, but also by higher, cortico-diencephalic and rhinencephalic systems concerned with the control of attention and emotional behaviour. The usefulness of such electrographic data for experimental psychology is pointed out.

REFERENCES

DEMPSEY, E. W., MORISON, R. S. and MORISON, B. R. Some afferent diencephalic pathways related to cortical potentials in the cat. *Amer. J. Physiol.*, **1941**, *131*: 718-731.

FRENCH, J. D., VON AMERONGEN, F. K. and MAGOUN, H. W. Activating system in brain stem of monkey. *Arch. Neurol. Psychiat.*, Chicago, **1952** *68*: 577-590.

GANGLOFF, H. und MONNIER, M. Bestimmung der elektrischen Erregbarkeit von Cortex, Diencephalon und Rhinencephalon beim Kaninchen. *Pflügers Arch.*, **1955**, *261*: 421-433.

GASTAUT, H. Introduction à l'étude électroencéphalographique du comportement. *Le sud méd. et chirur.* **1954**, *87*: 3320-3329.

GASTAUT, H., NAQUET, R., VIGOUROUX, R. et CARIOL, J. Provocation de comportement émotionnels divers par stimulation rhinencéphalique chez le chat. *Rev. neurol.*, **1952**, *86*: 319-327.

HESS, R. Jr., KOELLA, W. P. and AKERT, K. Cortical and subcortical recordings in natural and artificially induced sleep in cats. *EEG Clin. Neurophysiol.*, **1953**, *5*: 75-90.

HESS, R. Jr. Bioelectrical and behavioral arousal with electrical stimulation of mesodiencephalic structures. *EEG Clin. Neurophysiol.*, **1954**, *6*: 528-529.

INGRAM, W. R., KNOTT, J. R. and WHEATLEY, M. D. Electroencephalograms of cats under various experimental conditions. *Anat. Rec.*, **1949**, *103*: 157.

INGRAM, W. R., KNOTT, J. R., WHEATLEY, M. D. and SUMMERS, T. D. Physiological relationship between hypothalamus and cerebral cortex. *EEG Clin. Neurophysiol.*, **1951**, *3*: 37-58.

JASPER, H. and AJMONE-MARSAN, C. Patterns of organisation in the central nervous system. *Res. Publ. Ass. nerv. ment. Dis.*, Dec. **1950**, Williams and Wilkins Co., Edit. Baltimore, **1952**.

LIBERSON, W. T. and AKERT, K. Hippocampal seizure states in guinea pig. *EEG Clin. Neurophysiol.*, **1955**, *7*: 211-222.

MAGOUN, H. W. Patterns of organisation in the central nervous system. *Res. Publ. Ass. nerv. ment Dis.*, Dec. **1950**, Williams and Wilkins Co., Edit., Baltimore, **1952**.

MONNIER, M. Action de la stimulation électrique du centre somnogène sur l'électrocorticogramme chez le chat (Réactions hypniques et réaction d'éveil). *Rev. neurol.*, **1950**, *83*: 561-563.

MORUZZI, G. and MAGOUN, H. W. Brain-stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

MORUZZI, G. and MAGOUN, H. W. Brain-stem reticular formation and EEG arousal reaction. *EEG Clin. Neurophysiol.*, **1950**, *1*: 110.

MURPHY, J. P. and GELLHORN, E. The influence of hypothalamic stimulation on cortically induced movements and on action potentials of the cortex. *J. Neurophysiol.*, **1945**, *6*: 341-364.

RINALDI, F. and HIMWICH, H. E. A comparison of effects of Reserpine and some barbiturates on the electrical activity of cortical and subcortical structures of the brain of rabbits. *An. N. Y. Acad. sc.*, **1955**, *61*: 27-35.

Reference: GANGLOFF, H. and MONNIER, M. Electrographic aspects of an "arousal" or attention reaction induced in the unanesthetized rabbit by the presence of a human being. *EEG Clin. Neurophysiol.*, **1956**, *8*: 623-629.

ANNOUNCEMENTS

ARCHIVES ITALIENNES DE BIOLOGIE

Rédaction: ISTITUTO DI FISIOLOGIA DELLA UNIVERSITÀ - Via S. Zeno, 13 - PISA (ITALIE)
Administration: F. VALLERINI - « SALA DELLE STAGIONI » - Lungarno Pacinotti, 1 - PISA (ITALIE)

Archives Italiennes de Biologie, inaugurated in 1882 by A. Mosso in Turin and continued by V. Aducco in Pisa, stopped publication in 1935. Within half a century, the *Archives Italiennes de Biologie,* in 94 volumes, had provided the most important channel for the Italian contributions to the biological sciences. Bizzozero, Golgi, Grassi, Luciani, Marchi, Mingazzini and Mosso all submitted their original works to this journal. The collection can be found in most of the important libraries devoted to Medicine and the Natural Sciences.

After an interruption of twenty years, publication is being resumed under the editorship of Giuseppe Moruzzi, professor of Physiology at the University of Pisa. The journal will be devoted to publication of original contributions to physiology in either French or English, according to the choice of the author.

Volume 95, the first of the new series, will appear in 1957. Four numbers per annum will be published. Annual subscription price, payable in advance, is U. S. A. $10. Remittances should be sent to: The Administration, *Archives Italiennes de Biologie* (F. Vallerini — « Sala delle Stagioni » — Lungarno Pacinotti 1, Pisa, Italy). [International money order].

INTERNATIONAL ABSTRACTS OF BIOLOGICAL SCIENCES

Honorary Editor: C. C. N. VASS, M.Sc., Ph.D., M.B., Ch.B.

The Council of Biological and Medical Abstracts Ltd. has decided to change the title of their journal *British Abstracts of Medical Sciences* to

International Abstracts of Biological Sciences

This decision results from two major developments. The first is an extension of coverage to a wider range of biological research subjects published in journals throughout the world, and the second is that the International Abstracts of Biological Sciences, with the co-operation of the specialist editors selected by the Institute of Scientific Information of the Academy of Sciences of the U.S.S.R. will include, as from the January 1957 issue, translations of the important Russian papers abstracted in the *Referativny Zhurnal Biologii* (Soviet Biological Abstracts) and *Referativny Zhurnal Biologischekoi Khimii* (Soviet Abstracts of Biological Chemistry), to be published simultaneously with their appearance in Russian.

International Abstracts of Biological Sciences abstracts the world literature in the following fields: Anatomy, Animal Behaviour, Biochemistry, Biophysics, Cytology, Embryology, Endocrinology, Epidemiology, Experimental Biology, Genetics, Haematology, Histochemistry, Histology, Immunology, Microbiology, Nutrition, Odontology, Parasitology, Pathology, Pharmacology, Physical Anthropology, Physiology, Radiation Effects, Toxicology and Viruses.

International Abstracts of Biological Sciences is published for the Council of Biological and Medical Abstracts Ltd. by Pergamon Press, London and New York, *on a non profit-making basis.*

THE RELATION BETWEEN THE STARTLE REACTION AND THE NON-SPECIFIC EEG RESPONSE TO SUDDEN STIMULI WITH A DISCUSSION ON THE MECHANISM OF AROUSAL[1]

LARS-ERIK LARSSON, Med. lic.

Department of Clinical Neurophysiology, Serafimerlasarettet, Stockholm, Sweden

(Received for publication: April 5, 1956)

INTRODUCTION

In an earlier work (Larsson 1953) the electroencephalographic responses to peripheral nerve stimulation were investigated in waking human subjects. Among the responses were found a number of waves which as a rule began with a surface negative wave with a latency of 50-90 msec. These waves, which were first observed by P. Davis (1939), are not confined to the region of the specific somatic projection area and they can also be obtained after stimuli of a type other than that of peripheral nerve stimulation. They have a maximum over the vertex (P. Davis 1939, Bancaud *et al.* 1953 and Y. Gastaut 1954).

These waves, which in what follows will be called the "non-specific response", have characteristics which seem to be compatible with the assumption that they are an arousal response. When analysing this assumption it is necessary to try to arrive at an exact definition of the term "arousal". The following preliminary consideration was therefore made.

In general an individual is regarded as showing signs of arousal when by his behaviour he displays increased interest in his surroundings, looks around him, listens or investigates, and as a whole has a more active attitude than before. During these processes there is undoubtedly going on a progressive arousal, but these signs show rather that the individual *has* woken up than that he *is* waking up. It is reasonable to assume the existence of behavioural reactions which are better connected to the increase in the degree of wakefulness and which thus appear simultaneously with the arousal. The general muscular startle reaction (the startle pattern) which has been described by Strauss (1928) as well as by Landis and Hunt (1939) may be assumed to be a response of this type with regard both to its latency and duration and to its behavioural characteristics. It would therefore be possible to call it an arousal response. Responses which in comparable parts have the same characteristics as the muscular startle reaction might then be described as arousal responses. In order to investigate whether the non-specific EEG waves could be thus described, they have been systematically compared in this work with the blink component in the muscular startle reaction. A comparison between these two responses has been carried out earlier by, in particular, Bancaud *et al.* (1953). Among other things they showed that the startle blink and the non-specific EEG response are in several respects independent of each other.

MATERIAL AND METHODS

The experiments were carried out on 53 adult waking subjects, of both sexes. The subjects sat leaning back comfortably in an armchair. They knew that the intention was to investigate the reaction of the brain to different stimuli but that this would not involve any discomfort.

The blink component in the muscular startle reaction was chosen as an index of that reaction owing to its sensitivity and to the possibility it offered of simultaneously checking the blinking artefacts in the EEG record. It was led off from the skin above m. orbicularis oculi. In addition to the startle blink, which has a constant latency, a secondary blink is often recorded (Peak 1933). In cases where the startle blink is not strongly pronounced or is lacking altogether, this second-

[1] A preliminary report of these results was presented at a meeting of the Swedish Society for Clinical Neurophysiology on Dec. 4, 1954.

ary blink may be misinterpreted (fig. 1). Its latency is, however, normally considerably longer and varying, and this makes it easy to distinguish it from the startle blink.

Unless otherwise stated, the EEG response was recorded between an electrode on the vertex and another 3-5 cm. behind. With more electrodes, it is as a rule possible to show a phase reversal at the vertex. This permits determination of polarity. In the figures which show only one EEG lead, a downward deflection denotes surface-negativity.

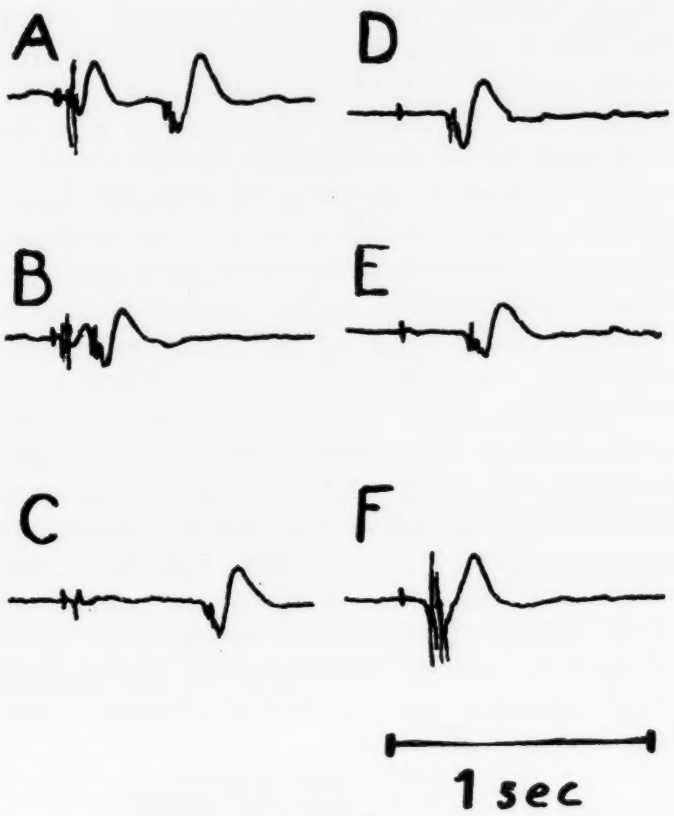


Fig. 1

The relations between the startle blink and the secondary blink to an acoustic stimulus. Stimuli following on each other with a frequency of 0.5/sec. It is seen how the startle blink gradually disappears whereas the secondary blink is unaffected as regards amplitude.

The electrodes were chlorided silver plates which were fixed with collodion in accordance with the usual technique.

The potential variations were led off to a Grass Model 3D EEG apparatus and recorded either with its ink-writer or with a cathode-ray oscillograph which was connected to its amplifier. In certain experiments two Grass pre-amplifiers Model P4 for connection to the cathode-ray oscillograph were used instead. As a rule the short time-constants of the apparatus (0.15 sec.) were used in order to reduce slow potential variations in the record. In the photographic records 10 cathode-ray sweeps were always superimposed to give a picture. At the beginning of the experiment the subject was told to blink strongly several times in order to ensure that no blink artefacts could appear in the EEG record. During the experiment the subject had his eyes open in order to reduce spontaneous activity in the EEG.

The stimulator was a Grass Model 3C, which was started by a square-wave generator. It operated at a preset frequency during the time occupied by the square wave. As the duration of the square waves was variable, it was thus possible to obtain pulses of predetermined number and frequency. The generator in its turn was started by a delay circuit.

Unless otherwise stated, the peripheral nerve stimulus was generally applied to the ulnar nerve at one elbow. At the output of the stimulator the stimulus pulses were rectangular and they generally had a duration of 1 msec.

The auditory stimulus consisted of a short click, which was obtained by connecting the stimulator to a pair of earphones.

Visual stimuli were delivered by a Kaiser Universal photostimulator which as a rule was triggered from the Grass stimulator. It gave an illumination of 9 megalux/m^2 at a distance of 5 cm. with the stimuli used. The duration of the flash was about 75 microsec.

In certain experiments it was necessary to alter the type of the stimulation faster than could be done by hand. This was done with the aid of a sensitive relay which was controlled from the timer relay output of the Grass stimulator.

RESULTS

Latency. When the ulnar nerve is stimulated at the elbow, the latency for the startle blink varies between 35 and 45 msec. The latency to the initial surface negative wave in the non-specific EEG response varies between 50-90 msec. Sometimes the EEG response begins with a small surface positive wave. Its

latency is about 30 msec. For auditory stimuli the latencies are somewhat shorter. The latencies for visual stimuli varied between 40-50 msec. for the startle blink and 60-80 msec. to the surface negative wave. In one case the latency to the electro-retinogram was measured in order to get an idea of its magnitude with the strong stimuli used. It amounted to 14 msec.

Comparison. If account is taken of the inconstant minor surface positive wave in the EEG response the latencies are of the same order of magnitude for both responses.

Thresholds. The thresholds for both responses vary within wide limits from one subject to another. Thus, for example, stimulations of peripheral nerves which give strong direct muscle twitches may sometimes be entirely ineffective while in other cases clear responses arise after stimulations which are far below the threshold for a perceptible movement and which are subjectively barely perceived. In the last-mentioned cases the EEG response has a somewhat lower threshold than the blink. In a series of stimulations with the same subject the thresholds for both responses generally vary from one stimulation to another, so that sometimes no responses occur and at other times strong responses appear. These variations do not take a parallel course for both responses (fig. 2).

Comparison. The thresholds are different insofar as the EEG response may be obtained with somewhat weaker stimuli. Both responses may, however, be obtained with very weak stimuli. The wide threshold variations from case to case are also a similarity.

Frequency-sensitivity. In figures 3 and 4 are shown simultaneous recordings of the startle blinks and the EEG responses. The stimulus was applied to the ulnar nerve on one side and its frequency was 0.25/sec. (fig. 3) and 0.5/sec. (fig. 4). The figures are taken from the same experiment. It appears that the blink is somewhat more frequency-sensitive than the EEG response. This is the most common relation, though the opposite may occur.

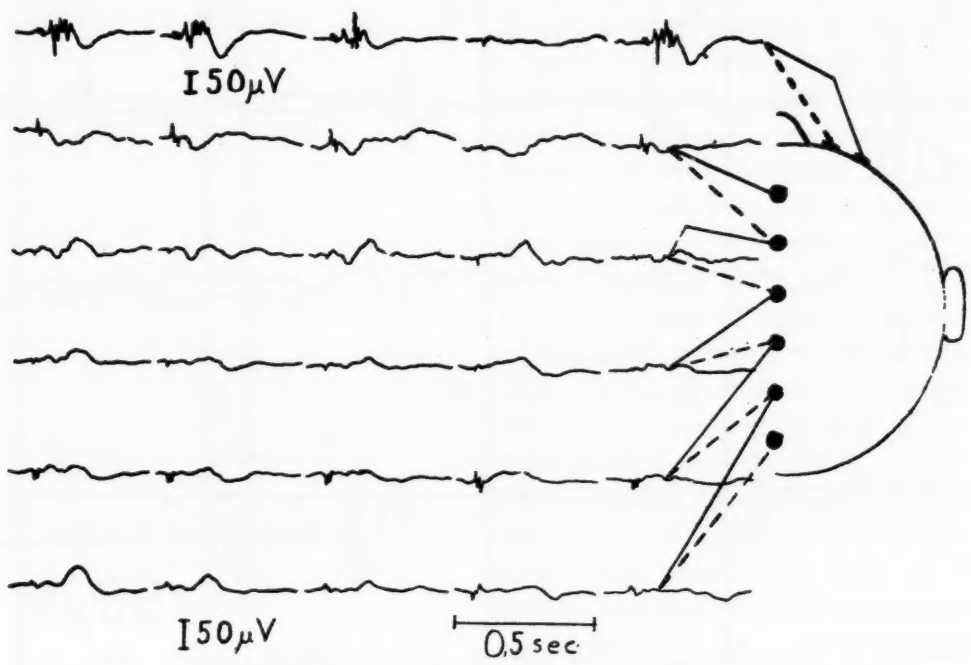


Fig. 2

Simultaneous recording of EEG response and blink response. Stimulus: sound + ulnar nerve. 4-6 pulses with a frequency of 500/sec. in each stimulus. Such a stimulus was given every 30 to 60 sec. Responses are selected from a long series. They show amplitude variations which are independent of each other.

Comparison. Although the blink is as a rule somewhat more frequency-sensitive than the non-specific EEG response, the sensitivity is of the same order of magnitude.

Specificity. Both responses can be obtained by stimuli of different modality (Landis and Hunt 1939, as regards the blink; Davis *et al.* 1939, as regards the EEG response). As a rule auditory and nerve stimuli give better responses than even strong visual stimuli. This observation should of course be considered with due regard to the difficulty of making intensity comparisons between stimuli of different modality.

As the responses are non-specific it was probable that occlusion would appear with simultaneous stimuli of different modality. That this assumption is correct is seen from the experiment illustrated in figure 5. In figures 5 A and B are seen the maximal responses after stimulations of the ulnar and median nerve respectively, and in figure 5 C the same responses after auditory stimulation. In figure 5 D the stimulations on the ulnar and the median nerves have been given simultaneously, in figure 5 E the ulnar stimulation and the auditory one were simultaneous and in 5 F the median and the auditory stimuli were simultaneous. In another experiment (fig. 6) where the submaximal responses after ulnar nerve stimulation were tested at varying times after maximal responses to sound, this blocking interaction persisted for at least 300 msec.

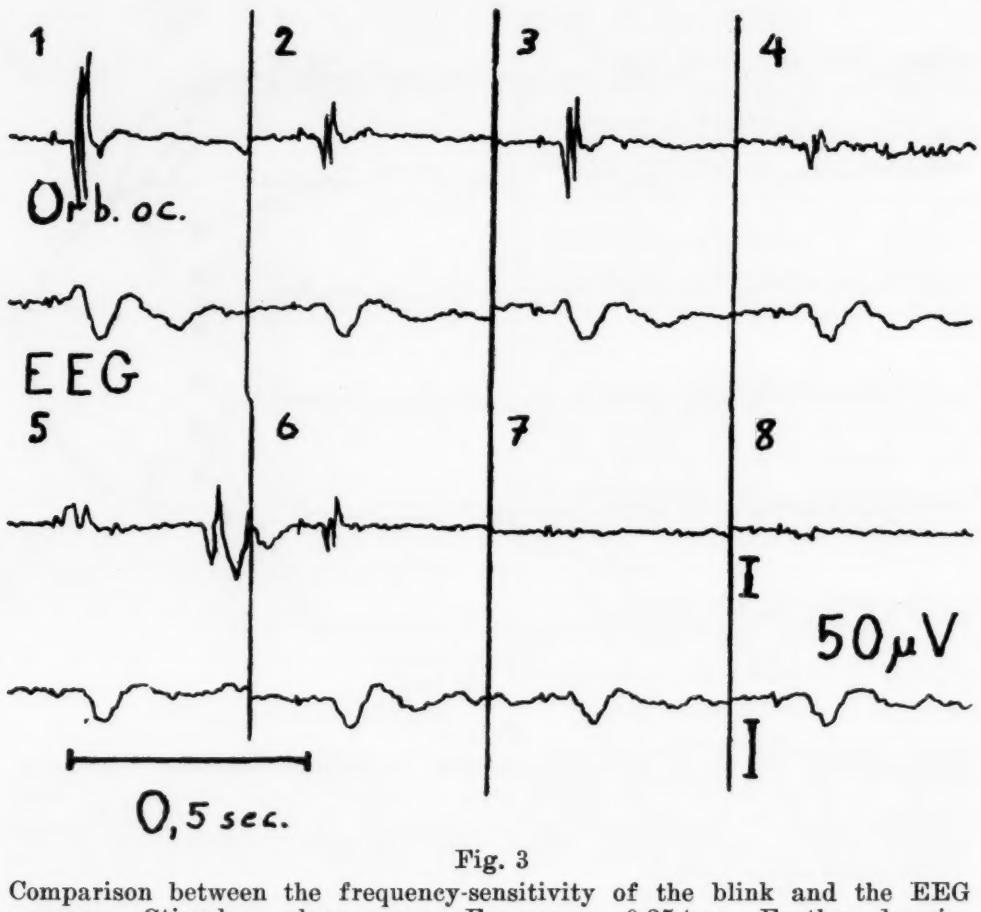


Fig. 3
Comparison between the frequency-sensitivity of the blink and the EEG response. Stimulus: ulnar nerve. Frequency: 0.25/sec. Further description in text. The figures 1, 2 ... etc. indicate the order in which the stimuli were applied.

If liminal stimuli of different modality are given simultaneously, there appears instead a facilitation of the responses. With simultaneous recording of the blink and the non-specific EEG response there may arise, at suitable stimulation strengths, facilitation for one response and occlusion for the other (fig. 7).

Comparison. The responses are similar in that they are non-specific, that they are poorly pronounced after visual stimuli and in the occlusive and facilitative phenomena which have been demonstrated.

Conditional reactions.[1]

Prosser and Hunter (1936) showed that the muscular startle reaction in rats can be made a conditional reaction, and this has also

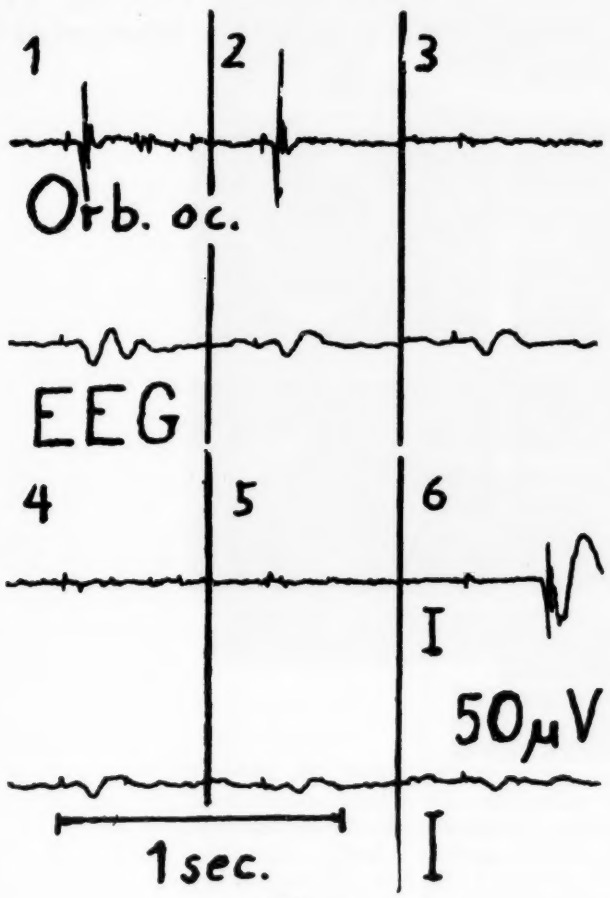


Fig. 4
Same as in figure 3, but with a stimulus frequency of 0.5/sec.

been shown in man by Landis and Hunt (1939). Experiments have therefore been carried out in order to discover whether this is also possible for the non-specific EEG response. Such an experiment is demonstrated in figure 8. In this experiment a weak sound stimulation which gave no response whatever was used as a conditional stimulus (CS) and a strong electrical stimulation of the ulnar nerve as the unconditional stimulus (US). The interval between CS and US was 1/2 sec. and each pair of stimulation was given with an interval of approximately 2 min. The last-mentioned interval was intentionally made variable in order to avoid any possible time-conditional reaction to this interval. The figure shows that at the 14th pair of stimulations the sound stimulus is possibly followed by an insignificant EEG response and that at the 21st pair the effect is certain. Moreover, a faint blink appears here. At the 26th and 27th pairs, the conditional responses have risen considerably in amplitude. The reinforcement with the electrical stimulus was discontinued after the 35th pair and it is to be seen how with the succeeding sound stimuli the responses are gradually extinguished. The conditional responses constitute augmented original responses to the conditional stimulus. This is shown by figure 9 C and D, where the recording has been done with a cathode-ray oscillograph. The records show the responses to a weak electrical stimulus before and after reinforcement by a strong sound stimulus. This type of conditional reaction has been called sensitization, "pseudo-conditioning" or "α-conditioning" (cf. Hilgard and Marquis 1940, for a review of the subject). It has been claimed that this type of conditional reaction occurs because the unconditional stimulus gives a long-term general increase of the excitability for all types of stimuli. This, it is claimed, results in strong responses to the stimuli irrespective of whether they have been paired previously with the unconditional stimulus or not. The existence of such a mechanism has been demonstrated *inter alia* by Bernstein (1934), Sears (1934) and Grether (1938).

It appears from the works cited above that sensitization may, at least under certain experimental conditions, play a part in the production of the type of conditional response which has been described in this study. In order to investigate whether this is the only factor at work, two types of experiment have been carried out. One of these types is illustrated in figure 9. In figure 9 A can be seen

[1] The term "conditioning" has a different meaning in a neurophysiological and in a psychological context. To avoid any possible misinterpretation we have preferred to use the term "conditional reaction" instead of "conditioned reaction" (cf. Pavlov, translated by Gantt, 1928, p. 79).

the superimposed result of a weak electrical stimulus on the distal phalanx of the thumb at the beginning of the experiment. Figure 9 B shows the same response recorded during a period when the electrical stimulus was interchanged at random with a strong sound stimulus with an interval of 30 to 90 sec. The record constitutes the total of the 31st to 40th electrical stimuli. In all, 42 sound stimuli had been given when the record was complete. With paired stimuli the conditional response is usually observed after about 20 paired presentations, and often earlier. No change can be observed here, however. On the following day the experiment was repeated with the same subject, with the difference that the electrical stimulus (CS) and the sound stimulus (US) were paired with an interval of 350 msec. Figure 9 C show the response to CS at the beginning of the experiment and figure 9 D the response after pairing with the sound stimulus (21-30 times). It will be seen that conditional responses have been obtained both for the startle blink and the non-specific EEG waves. The conditional responses were then extinguished, after which the electrical stimulus and the sound stimulus were given interchangeably in the same way as on the previous day. It was impossible to obtain a fresh increase of the response (fig. 9E). The experiment shows that the strong sound stimulus could not bring about an augmentation of the responses to the electrical stimulus if they were not paired with a fixed interval.

The other type of experiment started from the fact that conditional responses to a special stimulus are easily generalized, so that similar but not reinforced stimuli also give conditional responses. This is a normal occurrence in this type of experiment (Pavlov 1928, ch. IV). This fact can, however, also be interpreted as being due to a sensitization. If this interpretation is correct, it will not be possible to effect a differential inhibition (Pavlov 1928, ch. XVI) of the generalized conditional response. In figure 10 such an experiment is shown.

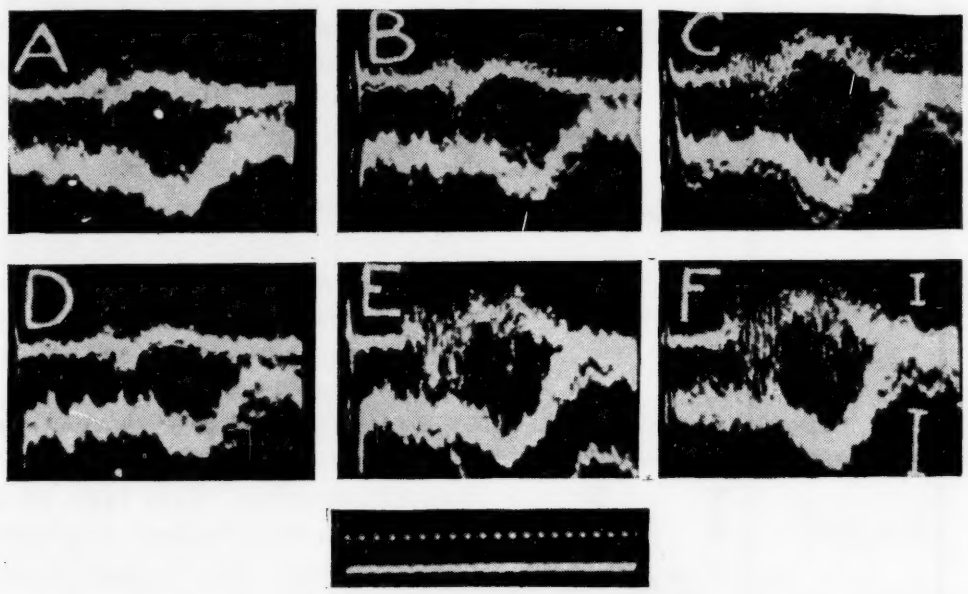


Fig. 5
Occlusion of responses. Stimulus: A. Ulnar nerve at the wrist. B. Median nerve, same side, at the wrist. C. Acoustic stimulus. D. Ulnar + median. E. Ulnar + acoustic. F. Median + acoustic. Time 10 msec. Cal. 50 μV.

A weak electrical stimulus was applied in turn to the distal phalanx of the thumb and little finger of the same hand. This stimulus produced little or no response (fig. 10 A, little finger, and fig. 10 B, thumb). After this had been repeatedly established, a strong sound stimulus was added to the little-finger stimulus 300 msec. after the latter. At the sixth paired presentation there appeared clear con-

ditional responses to the little-finger stimulus both in the EMG and in the EEG (fig. 10 C).[1] The stimulus on the thumb, which had never been reinforced, now also yielded clear responses — an example of generalization (fig. 10 D). Both finger stimuli were now repeated in such an order that it was impossible for the subject to predict in each particular case whether the next stimulus would be the ferential inhibition of the effect of the thumb stimulus had thus been obtained.

It is known that a recently established differential inhibition is a very unstable phenomenon (Pavlov 1928, ch. XXII). That this is also true of these conditional responses could be shown by making a pause of about 15 min. The stimulus on the thumb now once more produced its full effect (fig. 10 G), and

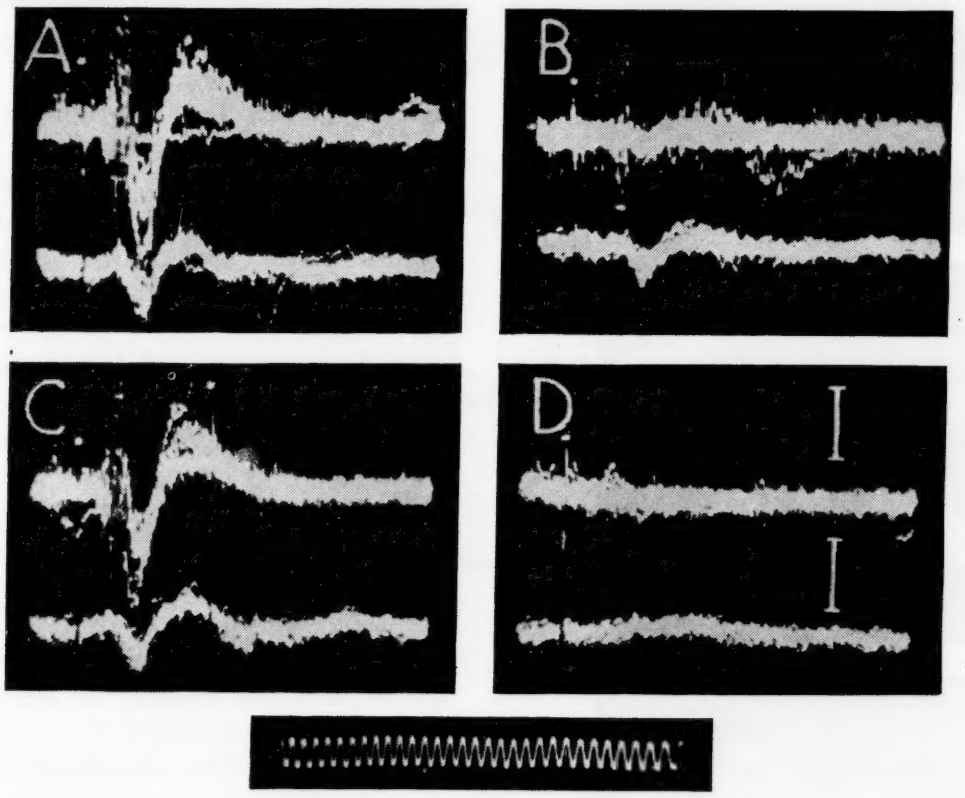


Fig. 6

Occlusion of responses to a weak electrical stimulus applied at varying intervals after a strong sound stimulus. A. Sound stimulus. B. Electrical stimulus. C. and D. Interval between the stimuli of 200 and 300 msec. respectively. In D the oscillograph sweep has been started about 230 msec. after the sound stimulus. The stimulus artefacts have been marked with small white dots. Time 20 msec. Cal. 50 μV.

"harmless" thumb stimulus or the ominous little-finger stimulus. After a total of 16 reinforced little-finger stimuli and 8 unreinforced thumb stimuli we can see how the former procedure gives conditional responses while the latter now is without effect (fig. 10 E, little finger, and fig. 10 F, thumb). This result was confirmed repeatedly. A dif-

a further 15 thumb stimuli and 7 reinforced little-finger stimuli were now required before the earlier differentiation could again be secured (fig. 10 H, little finger, and fig. 10 I, thumb).

It appears from these two types of experiment that pairing of the conditional and the unconditional stimulus is essential in order to bring about the conditional responses described. Sensitization in the ordinary sense of the word cannot be excluded, but it pro-

[1] This subject had been used in the same experiment three months earlier. This fact probably accounts for the relative ease with which the differentiation was established.

bably plays a subordinate role in the experimental conditions applied here.

Comparison. Both the blink and the non-specific EEG response can be obtained as the type of conditional reactions which are an augmentation of the original responses to the conditional stimulus. Generalization and differential inhibition proceed in parallel.

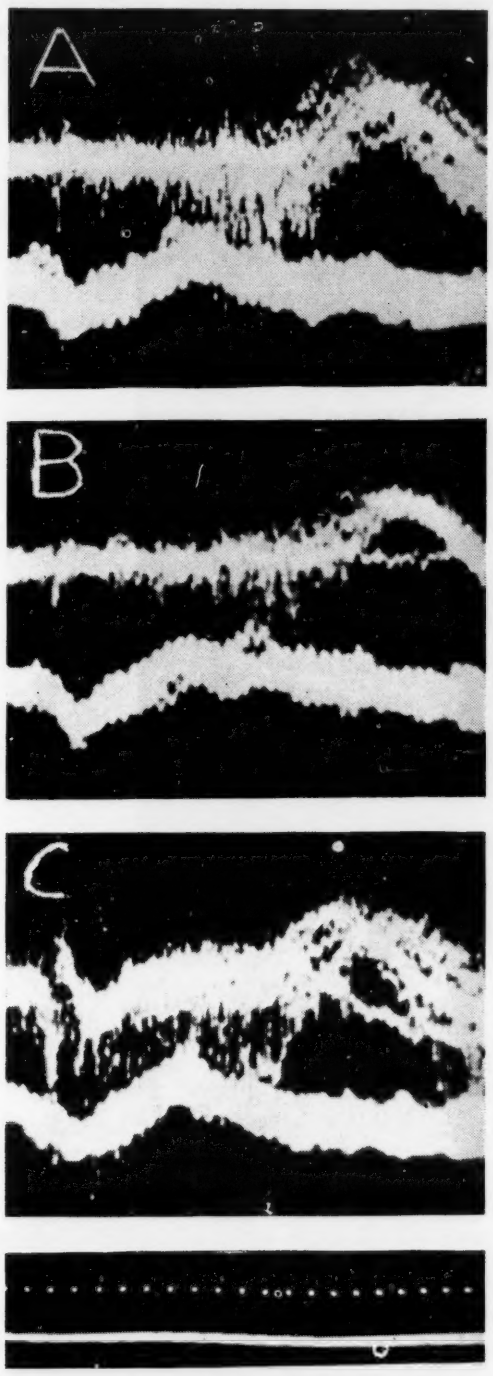


Fig. 7

Facilitation of the blink response and occlusion of the EEG response by simultaneous nerve and auditory stimuli. A. Electrical stimulation of ulnar nerve. B. Sound stimulus. C. Simultaneous electrical and sound stimuli. The late deflection in the upper sweep is a secondary blink. Time 20 msec.

DISCUSSION

It has been shown that latencies, stimulation thresholds and frequency-sensitivities for both the non-specific EEG response and for the blink component in the muscular startle reaction are, if not equal, at any rate of the same order of magnitude. Both responses are non-specific, occlusion and facilitation appear in a similar way and they can be made conditional reactions with the same characteristics for both of them. Such dissimilarities as are found are not important. An exact agreement as regards latencies is not, of course, to be expected for responses from structures so unlike as the cerebral cortex and the facial motor nucleus. If any other part of the muscular startle reaction than the blink component had been used as an index, the differences in the stimulation thresholds and the frequency sensitivity would have been greater. In a comparison such as this it is, however, most correct to use the most sensitive component.

To sum up, it is justifiable to draw from the above comparison the conclusion that the non-specific EEG response and the blink response are the results of activity in systems which are functionally very similar.

The responses are, however, independent of each other in the sense that it is not necessary for one of them to be present in order for the other to appear. The fact that one response can be facilitated and the other occluded with simultaneous stimuli of two different types points in the same direction.

Occlusion is generally regarded as being a sign of neuronal sharing. It is therefore probable that the afferent impulses of different modalities which can release the responses converge in a central non-specific system. As far as the EEG response is concerned, the experiments permit of no conclusions as to where this convergence occurs. As far as the blink is concerned, however, convergence must take place above the facial motor nucleus as it has been shown that the blocking interaction following maximal responses persists for at least 300 msec. As by

voluntary contraction the facial motorneuron can follow frequencies of at least 50/sec., which corresponds to an interval of 20 msec., it is impossible that the blocking takes place there.

It will now be of interest to see what indications the literature gives regarding the anatomical structures which are essential for the responses.

The muscular startle reaction.

Karplus and Kreidl (1914) observed startle reflexes (*ein lebhaftes Zusammenzucken*) in several of their decorticated apes after both tactile and acoustic stimuli. Widespread muscle reflexes, including lid closure, in response to acoustic stimuli were also observed by Forbes and Sherrington (1914) in cats decerebrated at the level of the anterior colliculus.

Culler and Mettler (1934) found a "slight startle" on acoustic stimuli in a decorticated dog, and human anencephalic monsters have been shown to have startle reactions on noises (Edinger and Fisher 1913).

It is clear, therefore, that the cerebral cortex is not essential for the startle reaction. This does not mean that the cortex is without influence. Muskens (1926), who made a systematic investigation on startle reflexes in cats after tactile and acoustic stimuli, writes that hemidecortication or unilateral section of the pyramidal tract abolished the reflex on the contralateral side. The reflex could, however, be evoked again if the animal was given

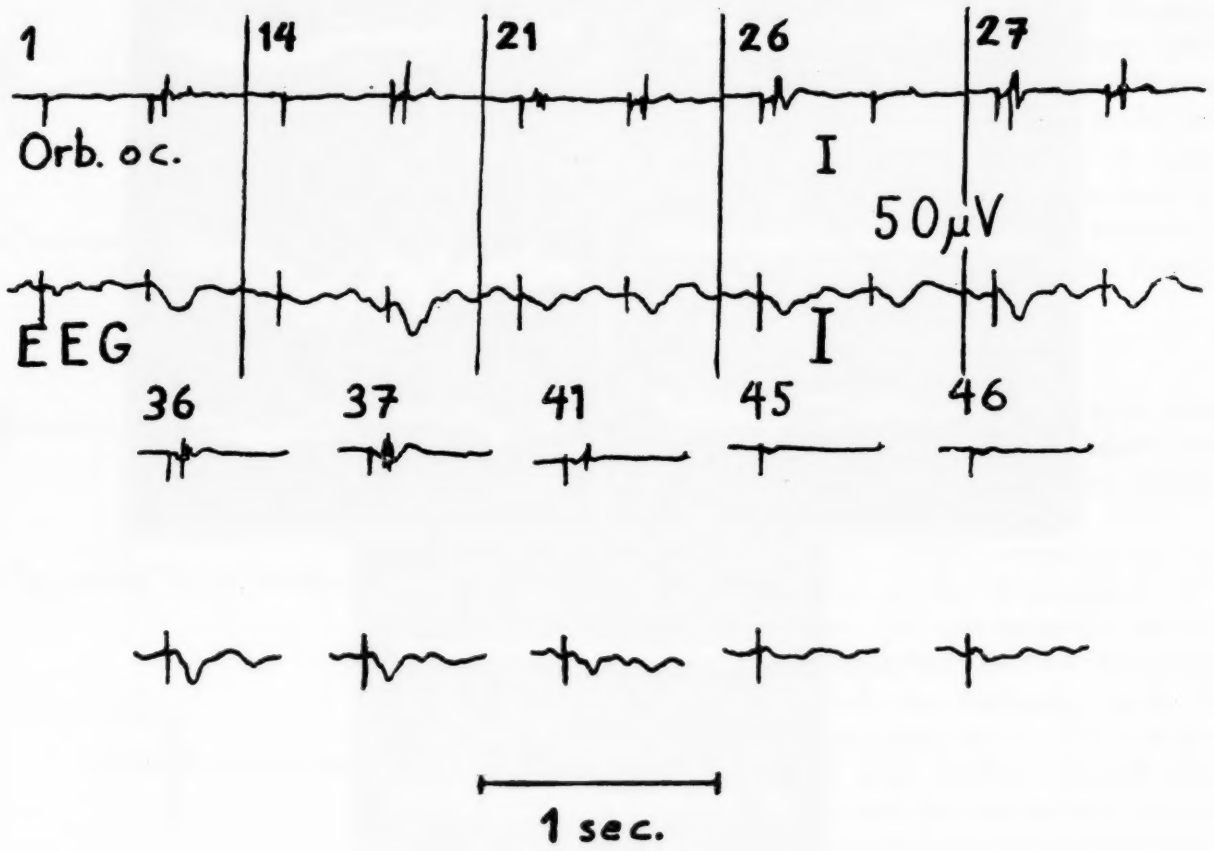


Fig. 8

The responses as conditional reactions. Stimuli: CS: weak sound stimulus. US: strong stimulus of ulnar nerve. The figures 1; 14 ... etc. indicate the order in which the paired stimuli were applied. Further description in text.

Metrazol or other cramp toxins. Haas *et al.* (1953), who investigated the reflex after Metrazol injection alone, concluded in agreement with Muskens that the motor cortex is important but not essential. They also considered that the specific sensory areas could be removed without affecting the reflex. Gastaut and Hunter (1950), who *inter alia* investigated myoclonic twitches after visual stimulation

and Metrazol injection, took the contrary view that bilateral ablation of the visual areas depressed the response while resection of the motor area did not give any effect.

Patients with various neurological diseases have been investigated by Strauss (1928). their startle pattern, provided spasm was not present. If spasm was present the effect was considerably increased on the affected side. Patients with Parkinson's disease and Huntington's chorea gave ambiguous results, while those exhibiting a pallidum syndrome are

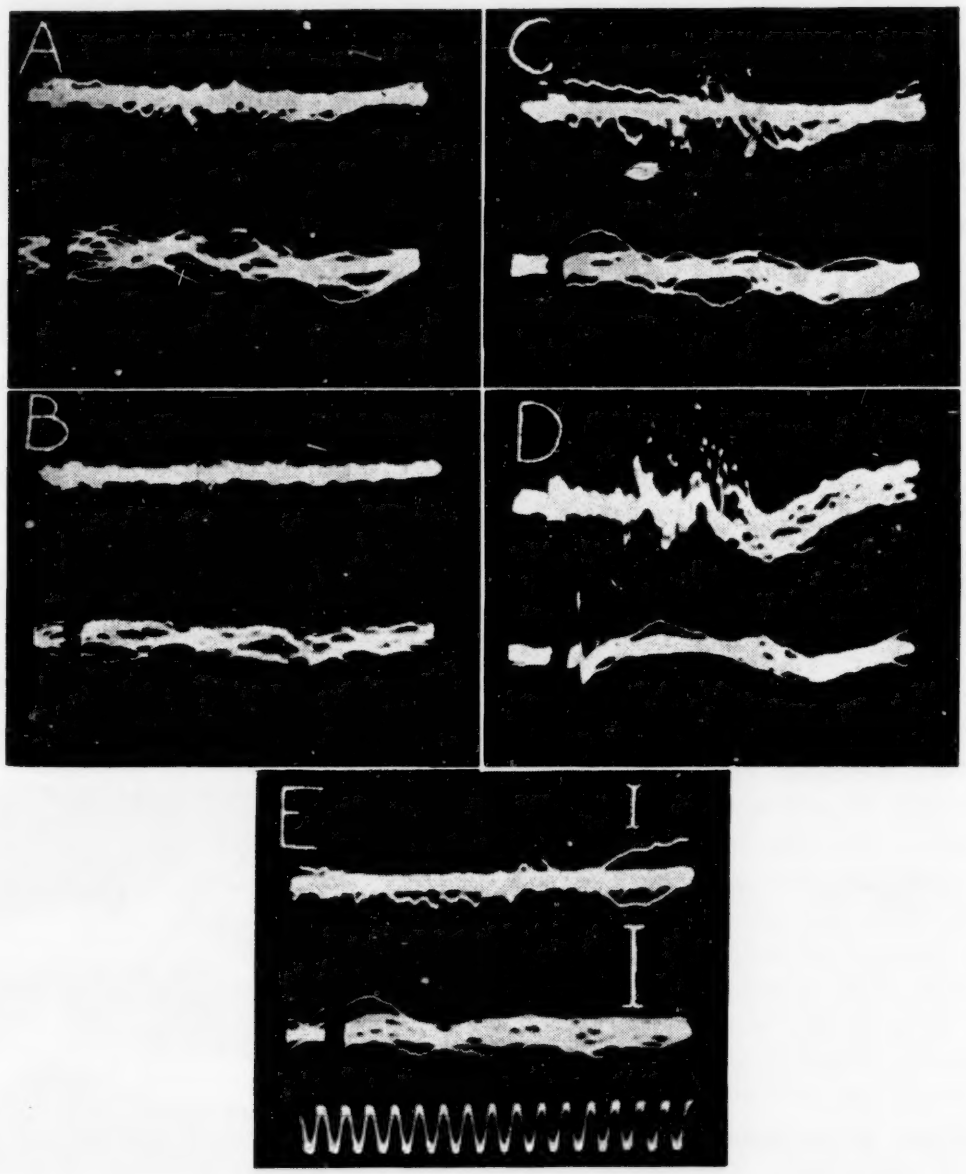


Fig. 9
Full description in text. The spike-like deflection in D (lower beam) immediately following the stimulus artefact is an artefact from the relay that changed the quality of the stimulus. Time 10 msec. Cal. 50 μV.

The results were summarized by him (1939) and included the cases which had been investigated in collaboration with Landis and Hunt. Among other things these showed that patients with slight hemipareses or positive Babinski did not show any lateralization in said to have yielded strong startle responses.

Muskens (1926) also investigated animals with injuries in parts of the brain other than the cerebral cortex. Bilateral injuries to the lemniscal pathways did not affect the reflex, whereas an animal which is said to have had

a probable injury to the cerebellar nuclei had an increased reflex. Injuries to the cerebellar cortex, however, are said not to have affected the reflex. Injuries corresponding to the reticular formation in the midbrain reduced the reflex considerably, but it did not definitely disappear until the medial portion of the reticulum in the transition between pons and medulla oblongata was destroyed. Then the reflex could no longer be obtained even after large doses of Metrazol. After destructions further caudally no response whatever was obtained on acoustic stimuli, while the response to tactile stimuli had changed its character. It thus appears as if the brain stem reticular system is a primary centre for the startle reflex. This system receives collaterals from the sensory pathways of different modalities (Starzl, Taylor and Magoun 1951 b; French, Verzeano and Magoun 1953) and there is evidence that various facilitatory and inhibitory areas exert much of their influence on the motorneurons through it (Lindsley, Schreiner and Magoun 1949 a and b). An influence from such areas may explain effects like the differential conditional reaction described here.

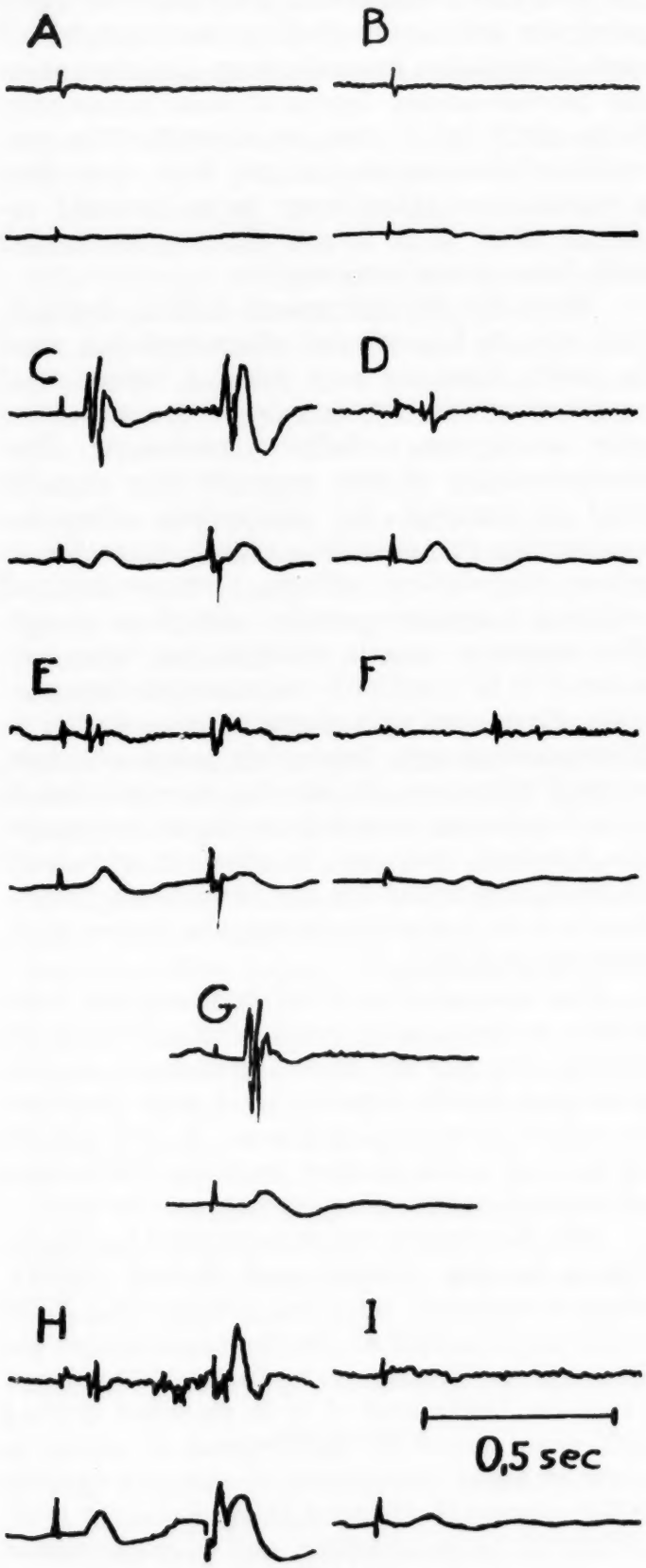


Fig. 10
Full description in text.

The EEG response.

The non-specific waves have been discussed in relation to the secondary response of Forbes, Morison and Dempsey (1936, 1939 and 1941) by several authors.

Davis *et al.* (1939) considered that the slow component of the K-complex, of which they considered the non-specific waves to be a part, corresponded to the secondary response obtained in animals, and Brazier (1949) holds the same view. The last-mentioned author has also (1954) shown that both the K-complex and the secondary response increase in certain degrees of anaesthesia.

The non-specific waves are as a rule localized to the vertex and, owing to this, Yvette and Henri Gastaut (1954) consider that it cannot correspond to the secondary response in animals which can always be led off from large areas of the cortex. In the works of Forbes and Morison and Dempsey (1936, 1939, 1941) the secondary response is described as predominantly surface-positive. On the basis of this it has been compared with the surface-positive component of the non-specific waves in man (Larsson 1953). Owing to the fact that the latency differences were great it was considered that the two responses could

not correspond to each other. In certain subjects an inconstant surface-positive wave precedes the surface-negative one. This was, however, considered as possibly corresponding to the secondary response obtained in animals.

The recent work of Purpura (1955) throws new light on these problems. The secondary response that he obtains in narcotized cats is a complex wave often introduced by a surface-negative component. Moreover, although it can be obtained over large parts of the cortex, it shows a maximum over the anterior portions of gyrus lateralis — a distribution which is similar to the maximum at the vertex which is as a rule obtained through the human skull. It seems possible that the human non-specific waves are related to Purpura's secondary response.

It has been shown in animals (Dempsey and Morison 1941; Starzl, Taylor and Magoun 1951; Purpura 1955), that single stimulation within the medial brain stem reticulum gives a cortical discharge with the same distribution as the secondary discharge evoked by peripheral stimulation and the same sensitivity to repeated stimulation. Further, the responses evoked by peripheral and reticular stimulation had a latency difference which was consistent with the conduction time between the two points of stimulation.

If the secondary discharge in animals is related to the non-specific waves in man, it is probable that the brain stem reticulum is essential for the occurrence of the non-specific waves, just as it is essential for the muscular startle reflex.

Arousal.

It has long been assumed that the K-complex and also the ''desynchronization'' of the EEG record after different stimuli constitute electroencephalographic arousal responses. The general validity of these assumptions has recently been questioned. Regarding the K-complex, Brazier (1954) writes that the term arousal response ''seems unfortunate since its major feature is that it occurs without arousing the subject.'' With regard to the desynchronization of the EEG record, Morison (1954) says that after high-frequency stimulation of intralaminar nuclei it is possible to obtain a desynchronization of the EEG without anything which is ''overtly similar to arousal'' being observed. It is, however, not necessary that the processes which appear in arousal should be strictly parallel in different parts of the brain. Such phenomena as sleep paralysis and somnambulism are examples of such dissociation in awakening. In other cases the increase in the degree of wakefulness may be so small that it does not show itself in perceptible behavioural changes. It is clear that a stimulation effect may be an arousal response even if it is not directly connected with behavioural arousal.

When the arousal process is to be defined, however, its behavioural characteristics must be used. Here we may select a behavioural response which appears on a common-sense view to express a definite awakening. The characteristics of this response may then be used as material for comparison when investigating the possible arousal character in other stimulation effects, irrespective of whether it appears parallel with these or not. The muscular startle reaction has been considered to be a suitable response for this purpose. Responses with characteristics similar to this reaction are, from this point of view, arousal responses. It may be objected that it would be better to call them startle responses. As, however, they can be obtained with very weak stimuli which are far from being ''startling'', it is preferable to use the wider term, arousal responses.

The non-specific EEG response has been shown to have very great similarities in its appearance to the blink component in the muscular startle reaction and may therefore be called an arousal response. It will now be of interest to see whether the usual EEG signs of arousal have corresponding similarities.

The K-complex was investigated by Davis, Davis, Loomis, Harvey and Hobart (1939). They considered that the non-specific EEG response is a part of the S-component of the K-complex. This has a maximum at the vertex (Brazier 1949) and if it is recorded during different stages of wakefulness it seems to show gradual transitions to the non-specific EEG waves (H. Gastaut 1954; Bancaud *et al.* 1953). It is non-specific, and is extinguished on repeated stimulation. Properties which can be interpreted as conditional reactions have

been described (Pampiglione 1953; Li, Jasper and Henderson 1952), although they have not clearly been shown to be of the same type as has been described for the startle blink and the non-specific EEG waves. To sum up, it is probable that the S-component in the K-complex is an arousal response, presumably from the same morphological system as the non-specific EEG waves but in a different excitatory state (cf. Jasper *et al.* 1952).

The blocking reaction also shows certain similarities to the startle blink. It is non-specific (Berger 1930), and it can be extinguished by repeated stimulation (Berger 1930; Travis and Egan 1938; Knott and Henry 1941). It can be obtained as a conditional response (Loomis, Harvey and Hobart 1937; Travis and Egan 1938; Knott and Henry 1941; Jasper and Shagass 1941). The conditional response is probably an augmentation of an original response to the conditional stimulus (Knott and Henry 1941). It therefore appears as if the blocking reaction is also an arousal response of a type similar to the startle blink.

Although in this study we have used the blink component in the muscular startle reaction as comparative material in order to analyze arousal, it does not mean that we consider that the whole process of awakening can be expressed with the aid of its characteristics. After arousal has begun, various orientational reactions often appear. These reactions, which are different from the primary muscular startle reaction, can be assumed to be necessary in order to maintain a degree of wakefulness already achieved and in order to facilitate further awakening, and may therefore be intimately bound up with the arousal process. On the analogy of Strauss's primary and secondary muscular startle reactions, one might therefore possibly be able to speak of primary and secondary arousal responses. Further investigations will, however, be necessary in order to elucidate these questions.

SUMMARY

1. A systematic comparison was made of the blink component in the muscular startle reaction and the EEG response which can be led off at the vertex after sudden stimuli.

2. The comparison showed that (*a*) the latencies are of the same order of magnitude, (*b*) thresholds and (*c*) frequency-sensitivity are, if not the same in each particular case, at any rate of the same order of magnitude. As a rule the blink has a somewhat higher threshold and a somewhat greater frequency-sensitivity than the EEG response. (*d*) Both responses appear after stimulations of different modality. (*e*) With two simultaneous stimulations of different type there appears, according to the strength of the different stimuli, facilitation or occlusion of the response, the EEG response may show one type of reaction while at the same time the blink shows another type. (*f*) Both responses can be obtained as conditional reactions. These consist in both cases of augmented original responses to the conditional stimulus.

3. Although the responses appear in a very similar manner they are independent of each other insofar as it is not necessary for one response to be present for the other to appear.

4. It is concluded that both responses arise in functionally similar systems.

5. The reticular activating system of the brain stem probably plays a considerable part in the creation of both responses.

6. The muscular startle reaction after sudden stimuli may be regarded as a sign of arousal. As the EEG response has proved to appear in a functionally similar way it is reasonable to regard it as an expression of an arousal mechanism.

7. It was shown that the unconditional stimulus cannot bring about an increase of the response to the conditional stimulus unless the two stimuli are paired with a definite interval. Moreover, the conditional reactions can be inhibited differentially. They cannot, therefore, be explained as being due to sensitization in the ordinary sense of the word (pseudoconditioning).

REFERENCES

BANCAUD, J., BLOCK, V. et PAILLARD, J. Contribution EEG à l'étude des potentiels évoqués chez l'homme au niveau du vertex. *Rev. neurol.*, **1953**, *89*: 399-418.

BERGER, H. Uber das Elektrenkephalogram des Menschen. Zweite Mitteilung. *J. Psychol. Neurol.*, **1930**, *40*: 160-179.

BERNSTEIN, A. L. Temporal factors in the formation of conditioned eyelid reactions in human subjects. *J. Gen. Psychol.*, **1934**, *10*: 173-197.

BRAZIER, M. A. B. The electrical fields at the surface of the head during sleep. *EEG Clin. Neurophysiol.*, **1949**, *1*: 195-204.

BRAZIER, M. A. B. The action of anaesthetics on the nervous system with special reference to the brain stem reticular system, in *Brain Mechanisms and Consciousness*, Oxford, Blackwell Scientific Publications, **1954**, p. 163.

CULLER, E. and METTLER, F. A. Conditioned behaviour in a decorticate dog. *J. Comp. Psychol.*, **1934**, *18*: 291-303.

DAVIS, H., DAVIS, P. A., LOOMIS, A. L., HARVEY, E. N. and HOBART, B. Electrical reactions of the human brain to auditory stimulation during sleep. *J. Neurophysiol.*, **1939**, *2*: 500-514.

DAVIS, P. A. Effects of acoustic stimuli on the waking human brain. *J. Neurophysiol.*, **1939**, *2*: 494-499.

DEMPSEY, E. W., MORISON, R. S. and MORISON, B. R. Some afferent diencephalic pathways related to cortical potentials in the cat. *Amer. J. Physiol.*, **1941**, *131*: 718-731.

DERBYSHIRE, A. J., REMPEL, B., FORBES, A. and LAMBERT, E. F. The effects of anesthetics on action potentials in the cerebral cortex of the cat. *Amer. J. Physiol.*, **1936**, *116*: 577-596.

EDINGER, L. und FISCHER, B. Ein Mensch ohne Grosshirn. *Arch. f. d. ges. Physiol.*, **1913**, *152*: 535-562.

FORBES, A. and SHERRINGTON, C. S. Acoustic reflexes in the decerebrate cat. *Amer. J. Physiol.*, **1914**, *35*: 367-376.

FORBES, A. and MORISON, B. R. Cortical response to sensory stimulation under deep barbiturate narcosis. *J. Neurophysiol.*, **1939**, *2*: 112-128.

FRENCH, J. D., VERZEANO, M. and MAGOUN, H. W. An extra lemniscal sensory system in the brain. *Arch. Neurol. Psychiat.*, Chicago, **1953**, *69*: 505-518.

GASTAUT, H. The brain stem and cerebral electrogenesis in relation to consciousness, in *Brain Mechanisms and Consciousness*, Oxford, Blackwell Scientific Publications, **1954**, p. 249.

GASTAUT, H. and HUNTER, J. An experimental study of the mechanism of photic activation in idiopathic epilepsy. *EEG Clin. Neurophysiol.*, **1950**, *2*: 263-287.

GASTAUT, Y. Negative spikes evoked at the vertex. Their psychophysiologic and pathologic significance. *EEG Clin. Neurophysiol.*, **1954**, *6*: 161.

GRETHER, W. F. Pseudoconditioning without paired stimulation encountered in attempted backward conditioning. *J. Comp. Psychol.*, **1938**, *25*: 91-96.

HAAS, A. M. L., LAMBROSO, C. and MERLIS, J. K. Participation of the cortex in experimental reflex myoclonus. *EEG Clin. Neurophysiol.*, **1953**, *5*: 177-186.

HILGARD, E. R. and MARQUIS, D. G. *Conditioning and Learning*. New York, Appleton-Century-Crofts, Inc., **1940**.

JASPER, H. H. and SHAGASS, C. Conditioning occipital alpha rhythm in man. *J. exp. Psychol.*, **1941**, *28*: 373-388.

KARPLUS, J. P. und KREIDL, A. Uber Totalextirpationen einer und beider Grosshirn Hemisphären an Affen. *Arch. Anat. Physiol.* (Abt. Physiol.), **1914**, 155-212.

KNOTT, J. R. and HENRY, C. E. The conditioning of the blocking of the alpha rhythm of the human electroencephalogram. *J. Exper. Psychol.*, **1941**, *28*: 134-144.

LANDIS, C. and HUNT, W. *The Startle Pattern*. New York, Farrar and Rinehart, Inc., **1939**.

LARSSON, L. E. Electroencephalographic responses to peripheral nerve stimulation in man. *EEG Clin. Neurophysiol.*, **1953**, *5*: 377-384.

LI, C. L., JASPER, H. and HENDERSON, L. The effect of arousal mechanisms on various forms of abnormality in the electroencephalogram. *EEG Clin. Neurophysiol.*, **1952**, *4*: 513-526.

LINDSLEY, D. B., SCHREINER, L. H. and MAGOUN, H. W. An electromyographic study of spasticity. *J. Neurophysiol.*, **1949**a, *12*: 197-205.

LOOMIS, A. L., HARVEY, E. N. and HOBART, B. Cerebral states during sleep as studied by human brain potentials. *J. Exper. Psychol.*, **1937**, *21*: 127-144.

MORISON, R. S., DEMPSEY, E. W. and MORISON, B. R. Cortical responses from electrical stimulation of the brain stem. *Amer. J. Physiol.*, **1941**, *131*: 732-743.

MORISON, R. S., in discussion on MAGOUN, H .W. The ascending reticular system and wakefulness, in *Brain Mechanisms and Consciousness*. Oxford, Blackwell Scientific Publications, **1954**, p. 18.

MUSKENS, L. J. J. *Epilepsie vergleichende Pathogenese, Erscheinungen, Behandlung*. Berlin, Julius Springer, **1926**.

PAMPIGLIONE, M. C. The phenomenon of adaptation in human EEG (a study of K-complexes). *Rev. neurol.*, **1952**, *87*: 197-198.

PAVLOV, I. P. *Lectures on Conditioned Reflexes*. New York, Liveright Publishing Corporation, **1928**.

PEAK, H. Reflex and voluntary reactions of the eyelid. *J. Gen. Psychol.*, **1933**, *8*: 130-156.

PROSSER, C. L. and HUNTER, W. S. The extinction of startle responses and spinal reflexes in the white rat. *Amer. J. Physiol.*, **1936**, *117*: 609-618.

PURPURA, D. P. Further analysis of evoked "secondary discharge"; a study in reticulocortical relations. *J. Neurophysiol.*, **1955**, *18*: 246-260.

SCHREINER, L. H., LINDSLEY, D. B. and MAGOUN, H. W. Role of brain stem facilitatory systems in maintenance of spasticity. *J. Neurophysiol.*, **1949**b, *12*: 207-216.

SEARS, R. R. Effect of optic lobe ablation on the visuomotor behaviour of goldfish. *J. Comp. Psychol.*, **1934**, *17*: 232-265.

STARZL, T. E., TAYLOR, C. W. and MAGOUN, H. W. Ascending conduction in reticular activating system with special reference to the diencephalon. *J. Neurophysiol.*, **1951**a, *14*: 461-477.

STARZL, T. E., TAYLOR, C. W. and MAGOUN, H. W. Collateral afferent excitation of reticular formation of brain stem. *J. Neurophysiol.*, **1951**b, *14*: 479-496.

STRAUSS, H. Das Zusammenschrecken: Experimentellkinematographische Studie zur Physiologie und Patophysiologie der Reaktivbewegungen. *J. Psychol. Neurol.*, **1928**, *39*: 111-231.

TRAVIS, L. E. and EGAN, J. P. Conditioning of the electrical response of the cortex. *J. Exper. Psychol.*, **1938**, *22*: 524-531.

Reference: LARSSON, L. E. The relation between the startle reaction and the non-specific EEG response to sudden stimuli with a discussion on the mechanism of arousal. *EEG Clin. Neurophysiol.*, **1956**, *8*: 631-644.

DEVELOPMENTAL STUDY OF THE ELECTROENCEPHALOGRAM OF THE DOG [1]

MARGARET S. CHARLES, M.S. and JOHN L. FULLER, Ph.D.
Division of Behavior Studies, R. B. Jackson Memorial Laboratory, Bar Harbor, Maine, U.S.A.

(Received for publication: February 23, 1956)

INTRODUCTION

A number of investigators have been interested in the developmental aspect of the electroencephalogram (EEG) and it is well known that in the human infant and child cortical potentials change with age. Although most of such work has been done on the human, a few papers have appeared representing work on other species. The white rat (Crain 1952), the guinea pig (Jasper *et al.* 1937), the kitten (Libet *et al.* 1941), and the monkey (Kennard *et al.* 1942) have been studied to some extent, but so far there has been no such study on the dog. The purpose of this investigation was twofold: (1) to extend knowledge of the developmental aspect of the electroencephalogram to another species, and (2) to demonstrate, if possible, electroencephalographic correlates of changes in behavior.

Much of the work involving the EEG of the adult dog has of necessity been done on anesthetized and/or curarized animals (Goldensohn *et al.* 1950; Swank *et al.* 1949). In this study the plan was to obtain the normal developmental pattern of the puppy EEG from birth to an age at which an essentially mature type of record could be obtained, using unanesthetized, unrestrained animals. Results were to be compared and correlated, if possible, with the known normal social and psychological development of the species.

TECHNIQUE

Scalp recordings were obtained from 12 animals in a total of 64 recording periods representing more than 11 total hours of recording. Two groups of dogs were used. The first consisted of normal (unanesthetized) animals and included 5 pups (one male and 4 females) from whom 57 scalp recordings were taken at various ages from one day to 8 weeks, plus one record from an adult male. The second group included 5 pups from three to 56 days of age (2 males, 3 females) and one adult female. Animals of this second group were anesthetized with Dial [2] (diallylbarbituric acid) and scalp recordings taken. Animals in the study included one adult Cocker Spaniel, one adult Chihuahua, and 3 purebred Basenji puppies. The remainder were various types of hybrids between Cocker Spaniel and Basenji.

A 4-channel, Model III Grass electroencephalograph was used. Both monopolar and bipolar recordings were made. Recordings were taken from within a shielded cage located in a quiet, dimly lighted room. A light mounted outside the cage could be directed on the subject. The size of the puppy head limited the number of electrodes. Five 9 mm. diameter Grass electrodes with flexible, insulated wires were attached to the shaved scalp and ears, using Redux paste as conductor and collodion as adhesive agent. Placement of electrodes was (fig. 1): 1, left occipital region (LO); 2, mid-frontal area (MF); 3, right occipital area (RO); 4, left ear; 5, right ear. Simultaneous monopolar recording was made from LO, MF, and RO areas using an ear as reference point; bipolar recording was made between LO and RO.

Small puppies were placed on a blanket over a warm hot-water bottle in a smooth metal tray. This resulted in some artifacts due to occasional limb or head movements but allowed the puppy complete freedom within the tray. Larger puppies were placed in a cardboard box or held on the lap of an as-

[1] This study is based in part upon a thesis submitted by Miss Charles to the University of Maine for the degree of M. S.

[2] Ciba Pharmaceutical Company.

sistant. Brief behavior observations were noted on the record as it was taken.

The dialized animals were injected either before or during recording. Dosage was 25-50 mg. per kg. of body weight given i.p. in small pups and IV in older pups.

Sensory stimulation while recording was accomplished by use of a pocket flashlight shone in the eye and a Galton whistle set at 5 and blown near the subject's head. Occasional attempts to elicit a cortical response were made by turning off the cage light or speaking. Subjects were picked up and held

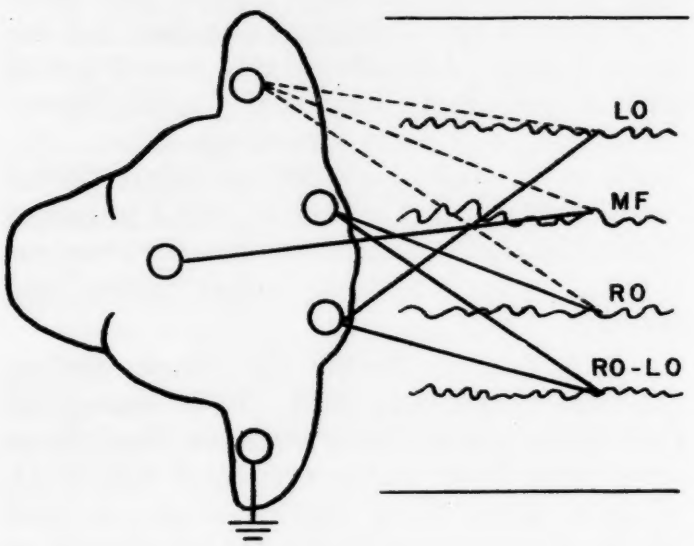


Fig. 1
Schematic diagram of puppy's head showing placement of scalp and ear electrodes as used throughout this study.

in an attempt to alert them and thus obtain a record during a state of wakefulness.

Gross inspection was made of each record in entirety. Detailed duration-frequency counts were carried out and plotted from samples of record at each age tested for 2 dogs of the normal group (34 records; the complete series on 2 animals). A count was made on each Dial record. Selection of portions for analysis was made according to predetermined rules in an attempt to obtain random sampling.

RESULTS

Characteristics of the normal EEG

General characteristics. Wave patterns in the EEG of the very young puppy were inconspicuous. In general, potentials generated were somewhat less than those found in human infants and children as demonstrated in Gibbs' Atlas (1945). As the puppies became older distinctive patterns of cortical activity emerged. Throughout the series of records amplitude was seen to vary from about 10 μV. to about 160 μV. the higher voltages being absent at very early ages. In general, all recordings from all areas were similar with the exception of slightly more activity at the frontal lead, which may have been due to scalp movement or eye potentials. Right and left occipital lobes showed no large differences.

Behaviorally it is difficult to determine whether the very young puppy is asleep or at a higher level of consciousness. However, certain behavioral criteria were used and the records annotated accordingly. Specifically, a newborn pup which remained quiet except for spasmodic twitching was considered "asleep" while a puppy which made movements such as crawling about in the tray or lifting the head was termed "awake".

At early ages (up to 3 weeks) these states of sleep and wakefulness were not distinguishable in the EEG. Differences appeared later and the sleep record then consisted of high potential, slow waves which came on gradually as the puppy appeared to go to sleep, and which disappeared abruptly upon alerting or awakening the pup suddenly. A stimulus which did not wake the animal did not disturb the pattern, however.

Alert, awake, or excited states were reflected in the older puppy by low amplitude, fast waves. There were, also, mixed patterns which fell between the two extremes of alertness and deep sleep.

Reactions to specific peripheral stimuli were variable, damping or "blocking" occuring at times but not consistently. However, sudden excitation produced increase in frequency and decrease in amplitude quite consistently.

EEG during first week of life. The EEG of the newborn puppy was characterized by flatness, low potentials and simplicity, as well as by numerous artifacts caused by apparently spontaneous twitching or jerking, which is

normal for the puppy. The record typically consisted of many rather flat sections interspersed with runs of low amplitude, sine waves at a frequency of about 14 c/sec. Distinct states of wakefulness and sleep were not distinguished in the EEG at this age and were also difficult to identify by observation. At the end of the first week the record was essentially the same as one or two days after

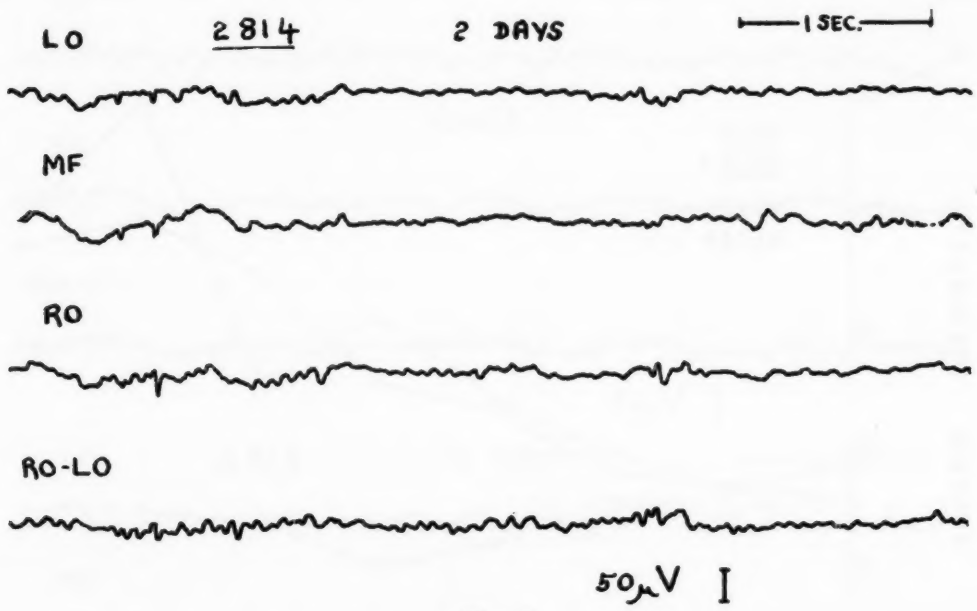


Fig. 2

Normal EEG records of a puppy at 2 days of age from LO, left occipital; MF, mid-frontal; RO, right occipital; and RO-LO, across right and left occipital leads.

birth (fig. 2). The frequency mode was 15 c/sec. for both wakefulness and sleep. Amplitude varied between 10 and 50 μV.

EEG during second week. During the second week the runs of small, smooth waves were still evident, as were some artifacts. By 10 days there were fewer flat periods. There was much moderate frequency, low amplitude activity in all areas. Amplitude ranged from 10 μV. to 45 μV. The frequency mode continued to be 15 c/sec. (.07 sec. wave duration).

EEG in third week. By the third week there were fewer twitching artifacts as the animals rested more quietly. Some random slow waves of indefinite shape appeared. All areas showed more activity and might show some 9-10 c/sec. sine waves which were greater in amplitude than they were earlier. It was in this period at about 16-18 days that the slow waves corresponding to sleep first occurred. These irregular, slow waves were opposed to the even, low amplitude activity which now occurred in all areas during waking. By 20 days a definite sleep pattern could be identified. Thus a marked change in frequencies and emergence of two distinct types of cortical activity representing wakefulness and sleep occurred at this age and the development during the next few weeks served to further separate and establish the two patterns, as may be seen in figure 3.

At this age there was also much even, 9-11 c/sec. activity which appeared when the dog was quiet. This was similar to the alpha wave frequency found in humans during periods of quiet wakefulness with eyes closed. This component was not seen in later records of the excited state nor in periods of deep sleep. The amplitude of these waves was about 40 μV. Some low potential activity of 10 μV. occurred but the larger sleep waves had a maximum near 85 μV. (fig. 4).

EEG during fourth week. At the beginning of the fourth week there were "resting" type waves (10-11 c/sec.) and slower waves of higher amplitude characteristic of sleep. Dur-

ing the week the amplitude of the sleep waves increased to as much as 130 μV. while the frequency decreased. By 28 days a pattern of fast, low amplitude waves corresponding to a state of alert wakefulness had emerged. During the fourth week of age four types of EEG could be distinguished in the puppy: (1) low, fast waves during wakefulness, (2) even, 10-11 c/sec. sine waves, (3) intermediate sections which included mixed frequencies and amplitudes, and (4) large, slow waves of deep sleep, which might carry small, fast waves superimposed on them.

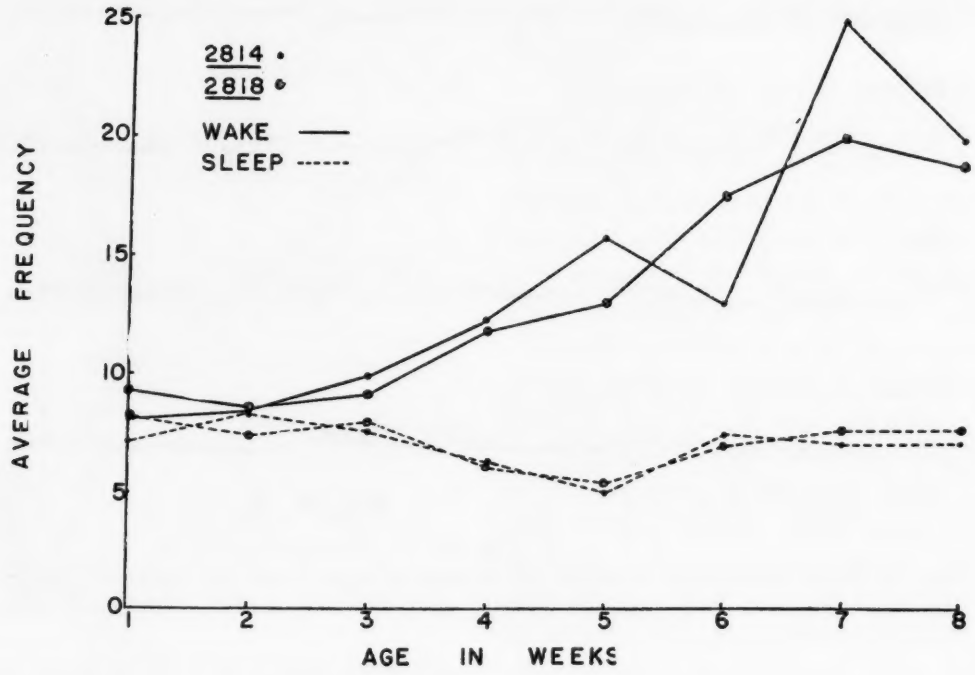


Fig. 3
Frequency of EEG waves (cycles per second) typical of sleep and wakefulness during 1 to 8 weeks of age in 2 puppies.

EEG from fifth through eighth weeks. Although detailed analysis was also made of records at each week from 5 to 8, the development after 4 weeks is conveniently treated as a unit.

The four types of cortical activity continued, the only changes being a gradual increase in frequency and decrease in amplitude in periods of alert wakefulness and a contrasting decrease in frequency and increase in amplitude in the waves typical of sleep. By 7 weeks amplitude varied from 10 to 155 μV., and the mode of the wakefulness frequencies had become 30 c/sec. or .03 sec. in duration. The range of the wakefulness pattern waves extended from 6.7 to 60 c/sec. (.15 to .02 sec.) while the sleep range was 1.7 to 30 c/sec. (.60 to .03 sec.) (see fig. 5). At eight weeks frequencies were grouped as in the previous three weeks. There was much EEG activity which was very fast and low in potential which reflected the alert, excited behavior of the puppy. All waves were less smooth and more complex. Resting type waves were mostly lacking and actually the puppies did not rest as during very early records. During the last two weeks of recording (7 and 8 weeks of age) the pups were typically either asleep or else awake and very alert.

It has been reported in the literature (Girden 1948) that Dial does not affect the EEG. Since records from unanesthetized adults showed many muscle artifacts, a series of records were taken from animals anesthetized with Dial. Such records taken at intervals from one day to 8 weeks were similar to those taken from unanesthetized animals of similar ages. Apparently the Dial had little effect

on the normal EEG as was expected. Supplementing this, a record was taken from adult dog anesthetized with Dial. This record was essentially similar to that of the eight week old puppy. It was concluded that the EEG of the puppy at 8 weeks of age is essentially similar to that of an adult dog.

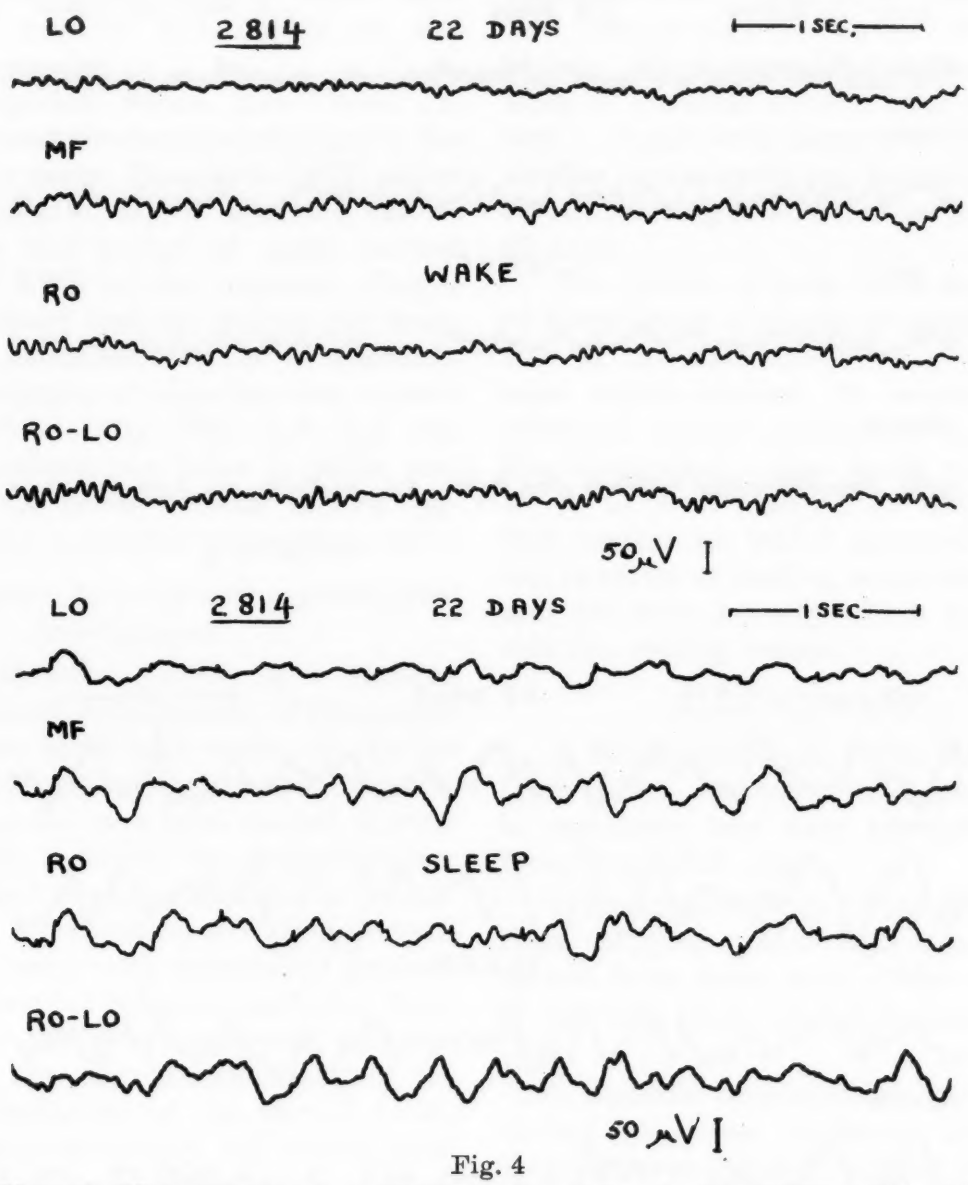


Fig. 4
Normal EEG records of a puppy at 22 days of age during states of wakefulness and sleep.

DISCUSSION

A. *Species comparisons*

It appears from the results of this study that the development of the EEG in the puppy is similar to that of other species in that increase in age from birth is accompanied by increased cortical activity. In the study of cerebral electrical potentials in the guinea pig by Jasper *et al.* (1937), it is reported that brain potentials first appeared in the electrocorticogram (ECG) at 48-56 days of gestation which is approximately three weeks before birth. This species was studied at intervals from this age until adulthood but no clear ontogenetic trend in characteristic frequencies was observed, although average amplitude showed an irregular but definite increase with age.

Electrocorticograms taken from curarized young albino rats (Crain 1952) showed ir-

regular, low amplitude activity during the first week of life. By the seventh to tenth days regular, rhythmic and continuous activity appeared and the 10 day patterns were basically similar to those of the adult rat. progressing to amplitudes of 20-100 μV. and frequencies of 1-35 c/sec. in the 19-25 day old animal. The adult cat record showed a dominant frequency of 40 c/sec.

Kennard and Nims' study on *Macaca mu-*

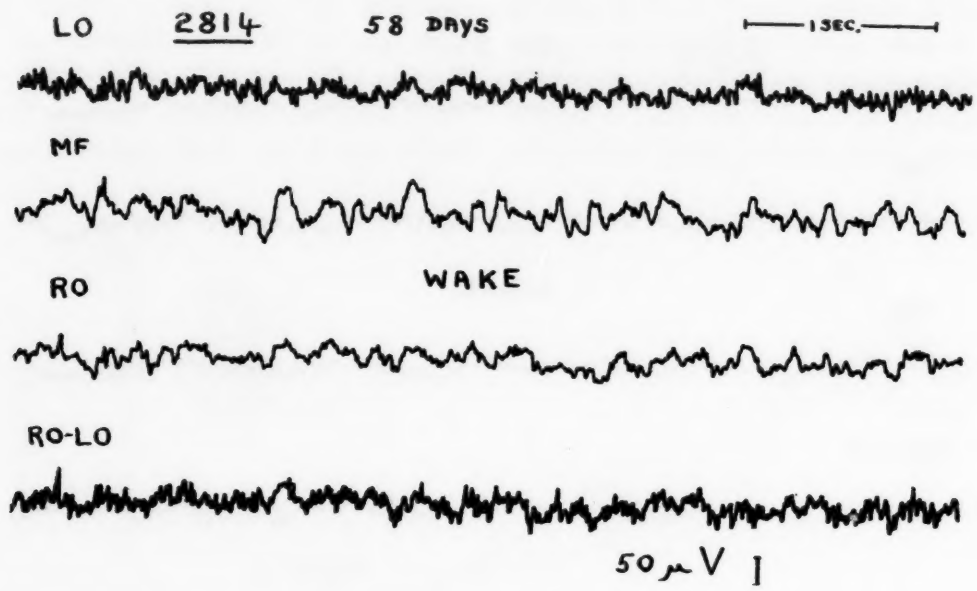


Fig. 5
Normal EEG records of a puppy at 58 days of age during states of wakefulness and sleep.

Both amplitude and frequency increased with age from birth to 10 days.

The ECG of the kitten as demonstrated by Libet *et al.* (1941) underwent similar developmental changes, beginning with low amplitude (5-20 μV.) random activity and *latta* (1942) had similar results. The scalp recorded EEG during the first postnatal week revealed low potentials and little activity. By four weeks both amplitude and rate increased and there was a distinction between states of wakefulness and sleep. This trend

continued until 6-12 months of age when there was a slight decrease in amplitude.

The development of the EEG in the human infant and child as demonstrated by Gibbs (1945) and discussed by Walter (1953) follows a similar pattern of low amplitude, low frequency, irregular activity which later becomes more regular and higher in amplitude and frequency.

In these species which have been investigated the most pronounced changes in the EEG occur very early. Kennard (1942) states that development of motor function occurs largely during the period of most marked change in the EEG of the monkey. Jasper *et al.* (1937) report that the guinea pig brain first exhibits electrical activity at the time when the maturation of high nervous centers is indicated behaviorally. The fact that this occurs in the guinea pig prior to birth probably reflects the precociousness of this species which is born in a relatively mature state.

B. *EEG in relation to social and psychological development*

Scott and Marston (1950) in a detailed study of the normal development of the puppy found that from birth to 2 weeks of age the pup lives a relatively vegetative existence. By two weeks of age the eyes have opened in most animals, and by 3 weeks the majority have the ears open and the animals react to sound. Following this, socialization and development of motor skills ensue with subsequent gradual emergence of complex behavior patterns. Scott emphasizes that the most important and critical period for the normal adjustment of the puppy is the beginning of the period of socialization at approximately 3½ weeks with "maturation of sensory, motor, and memory capacities apparently coinciding with the first development of outside social relationships". It is at this same age of changing behavioral development that the EEG of the puppy begins to change, as the patterns of cortical activity associated with different behavioral states become established.

In studying the advent of the conditioned reflex (CR) in the same species, Fuller *et al.* (1950) attempted to condition very young puppies. It was found that there was no reliable evidence of conditioning to light and sound before 18 days; sporadic positive responses occurred from 18 to 20 days; but after 20 days the CR was definite and fairly predictable. Fuller suggests that "a fundamental change in neural organization of the puppy occurs during the latter part of the third postnatal week", and that "the results can be best interpreted in terms of maturational change, which probably involves the development of cerebral control over the motor centers". James and Cannon (1952) carried out similar experiments and found the earliest age of conditioned orientation in the puppy to be 21 days.

The results of both these studies and that of Scott imply a change in neuronal organization at the time the EEG is undergoing its most rapid change. It would appear that whatever neural mechanism is necessary for the conditioned reflex is the same as, is part of, or at least matures at the same time as that mechanism which operates in the changing rhythms of resting wakefulness and sleep, and the beta activity which apparently cancels the resting waves.

SUMMARY

1. Scalp recordings of the EEG were made from intact, unanesthetized puppies varying in age from two days to eight weeks, and from one adult dog.

2. Scalp recordings of the EEG were made from puppies under Dial anesthesia at intervals from three days of age to eight weeks of age and from one adult anesthetized with Dial.

3. Specific sensory stimulation of puppies during recording produced inconsistent results whereas general, sudden excitation consistently caused increase in frequency and decrease in amplitude.

4. Records of normal puppies under three weeks of age were low in amplitude and contained random low frequency activity. Patterns of wakefulness and sleep were indistinguishable in the EEG.

5. EEGs of normal puppies showed differentiation between sleep and wakefulness at about 18-20 days, the difference becoming marked by four to five weeks.

6. Very fast activity appeared as a definite

component of the normal EEG of alert puppies by five weeks.

7. Sleep waves were characterized by slow frequency and high amplitude; waves during wakefulness were characterized by higher frequency and low amplitude.

8. Four patterns of activity could be recognized in the puppy EEG: (*a*) very fast, low amplitude waves during excitation; (*b*) waves of medium amplitude and frequencies of 8-14 c/sec. found during resting; (*c*) intermediate waves of mixed amplitude and frequency not typical of wakefulness or sleep; (*d*) high amplitude, low frequency waves typical of deep sleep.

9. Light to moderate Dial anesthesia did not markedly affect the spontaneous electrical activity of the brain. The eight week EEG of the puppy anesthetized with Dial resembled that of the adult anesthetized with Dial.

10. The most marked change in the puppy EEG occurred at the period of most marked change in physical and social development and at the time that relatively stable conditioned reflexes can be established.

11. Generally speaking, maturational changes in the EEG of the puppy are similar to those described in a number of other mammals.

REFERENCES

CRAIN, S. M. Development of electrical activity in the cerebral cortex of the albino rat. *Proc. Soc. Exp. Biol. Med.*, **1952**, *81*: 49-51.

FULLER, J. L., EASLER, C. A. and BANKS, E. M. Formation of conditioned avoidance responses in young puppies. *Amer. J. Physiol.*, **1950**, *160*: 462-466.

GIBBS, F. A. and GIBBS, E. L. *Atlas of Electroencephalography*. Cambridge, Mass., Addison-Wesley Press, 2nd printing, **1945**, 221 pp.

GIRDEN, E. The electroencephalogram (EEG) in *curarized* mammals. *J. Neurophysiol.*, **1948**, *11*: 169-174.

GOLDENSOHN, E. S., BUSSE, E. W., SPENCER, J. N., DRAPER, W. B. and WHITEHEAD, R. W. Studies on diffusion respiration. VII. The cortical electrical activity of dogs. *EEG Clin. Neurophysiol.*, **1950**, *2*: 33-40.

JAMES, W. T. and CANNON, D. J. Conditioned avoiding response in puppies. *Amer. J. Physiol.*, **1952**, *168*: 251-253.

JASPER, H. H., BRIDGMAN, C. S. and CARMICHAEL, L. An ontogenetic study of cerebral electrical potentials in the guinea pig. *J. exp. Psychol.*, **1937**, *21*: 63-71.

KENNARD, M. A. and NIMS, L. F. Changes in normal electroencephalogram of *Macaca mulatta* with growth. *J. Neurophysiol.*, **1942**, *5*: 325-334.

LIBET, B., FAZEKAS, J. F. and HIMWICH, H. E. The electrical response of the kitten and adult cat brain to cerebral anemia and analeptics. *Amer. J. Physiol.*, **1941**, *132*: 232-238.

SCOTT, J. P. and MARSTON, M. Critical periods affecting the development of normal and mal-adjustive social behavior of puppies. *J. genet. Psychol.*, **1950**, *77*: 25-60.

SWANK, R. L. and WATSON, C. W. Effects of barbiturates and ether on spontaneous electrical activity of dog brain. *J. Neurophysiol.*, **1949**, *12*: 137-160.

WALTER, W. G. Electroencephalographic development of children. In U.N.W.H.O. Study group on psychobiological development of the child. *W.H.O. Proc. First Meet.*, Geneva, **1953**, pp. 139-170.

Reference: CHARLES, M. S. and FULLER, J. L. Developmental study of the electroencephalogram of the dog. *EEG Clin. Neurophysiol.*, **1956**, *8*: 645-652.

FREQUENCY OF PHOTIC STIMULATION AS A VARIABLE IN THE ACTIVATION OF EXPERIMENTAL CONVULSIONS

KENNETH A. KOOI, M.D.[1] and EDWARD C. BECK, Ph.D.[2]

With the technical assistance of CHARLES I. LEWIS [3]

Neurology Section, Department of Psychiatry, University of Utah College of Medecine, and the Neurology and Psychology Services, Veterans Administration Hospital, Fort Douglas Division, Salt Lake City, Utah

(Received for publication: February 6, 1956)

INTRODUCTION

It has been observed that photic stimulation will precipitate seizures and paroxysmal discharges in certain light-sensitive epileptics (Gowers 1881; Walter *et al.* 1946; Cobb 1947). From clinical studies it is clear that variation of the frequency of the stimulus, as well as of other parameters, affects the response (Walter and Walter 1949; Schwab and Abbott 1951; Van Buskirk *et al.* 1952; Marshall, Walker and Livingston 1953). The literature pertinent to physiological mechanisms in visual activating techniques has been reviewed by Brazier (1953) who notes that clinically "flash-rates of about 15 c/sec. are potent activators in most cases". However, she adds that there are also cases activated by a single flash and those activated by almost any flash rate.

Experimental convulsions influenced by photic stimulation were first reported by Clementi (1929). The experimental preparation was a non-narcotized dog with strychnine applied to the visual cortex. The first electroencephalographic observations were made by Gozzano (1935) who demonstrated that light stimulation resulted in an increase in spike activity from the strychninized striate area of a rabbit with subsequent initiation of brief seizures. Gastaut and Hunter (1950) noted that single flashes of light would evoke spikes from the strychninized visual area of the cat but that if the frequency of stimulation was "sufficiently high" the cortex responded to only the first flash of the series. Seizures were not obtained. Terzian and Terzuolo (1953) confirmed the fact that spikes arising from a strychninized area striata can be driven by photic stimuli and that their repetition rate can be greatly increased as a result. Seizures occurred in their preparations (rabbits) which were observed to arise in the visual area, spreading later to the contralateral visual zone and finally to motor centers.

In the present study penicillin was used to initiate seizure discharge. The use of penicillin is suggested by the studies of Walker and Johnson (1945) and Borkowski and Forster (1947). The activity of the penicillin-induced focus was then observed systematically under varying frequencies of photic stimulation.

With the increasing use of photic stimulation as an activating technique more information is needed on the nature of the response of such a focus to variations in the afferent stimulus. Furthermore, characteristic frequency sensitivities may emphasize similarities or differences between clinically observed photogenic epilepsy and activated experimental convulsions and possibly help to clarify the mechanism of the activating process.

METHOD

Thirty-four adult cats were used in the experimental series. The electroencephalograms were taken in the following manner: under intraperitoneal Nembutal anesthesia the scalp was reflected and burr holes drilled bilaterally with a ♯ 6 dental burr in anterior,

---

[1] Instructor in Psychiatry (Neurology), University of Utah College of Medicine, Director, Electroencephalographic Laboratory, Veterans Administration Hospital, Fort Douglas Division.

[2] Research Instructor in Psychiatry (Psychology), University of Utah College of Medicine, Clinical Psychologist, Veterans Administration Hospital, Fort Douglas Division.

[3] Research Technician (Animal Anatomy), Veterans Administration Hospital, Fort Douglas Division.

central, and posterior positions. These were routinely placed 7 mm. from the midline and 1.5 cm. apart in anterior-posterior dimensions. No. 2 metal tapping screws to which an insulated wire had been previously soldered, were then inserted into the 6 burr holes. A polyethylene cuff was threaded over the wire coming to rest around the screw on the surface of the skull. This cuff was then filled with acrylic powder and several drops of acrylic liquid were applied. The electrode was thus fixed securely to the skull and adequate insulation obtained. The 7 leads were brought out through the midline incision, the incision being closed on either side with catgut sutures. At the time of the initial operation a trephine opening was made over the visual area. Two or three days following the initial operation penicillin was injected immediately subcortically through this opening. Early this was carried out in the alert animal with physical restraint, under local 1 per cent procaine infiltration. In the last 12 preparations the animal was tracheotomized under ether anesthesia, curarized with 1-2 mg. per kilogram of tubocurarine i.m., and placed under artificial respiration. Procaine was again locally injected in the skin area above the trephine opening, the skin incision reopened and the penicillin injected. The penicillin injection was carried out with the aid of a stereotaxic instrument so that depth from the cortical surface could be controlled. One to two-tenths of a cubic centimeter of Pfizer penicillin in sesame oil with 1 per cent aluminum monostereate was routinely injected 1-2 mm. below the cortical surface. The penicillin was injected after the animal regained an "alert" electroencephalographic pattern. At least one hour was allowed for exhalation of the anesthetic agent.

In order to prevent variations in light intensity arriving at the retinae it was necessary to consider head movement, closure of the nictitating membrane, blinking, and pupillary constriction and dilatation. In the early experiments head movement was controlled by a metal frame head holder which prevented lateral and vertical deviations. Blinking was prevented by small wire lid retractors, and 1 per cent homatropine gave maximal dilatation of the pupils. The nictitating membranes were routinely resected at the initial operation. The difficulties due to head movement and blinking were later obviated by the use of tubocurarine and artificial respiration, the animal being placed in a stereotaxic instrument, 1 per cent procaine having previously been injected beneath the orbits and around the external auditory canals. The photic stimulator employed was a Grass, Model PS-1, with a high intensity flash of approximately 10 μsec. duration. The lamp was adjusted so that its center was level with the animal's eyes and its face perpendicular to the line of vision, 15 cm. from the cornea. Background intensity remained constant during the experiment.

A control record was taken immediately before the penicillin injection so that possible changes in the pattern from drug effects or damage related to the electrode placement or trephination could be observed.

The photic stimulus was presented for varying periods, at a constant intensity. Several different frequency series were employed. In 7 experiments 22 different frequencies were used: ½, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 21, 24, 27, 30, 40, 50, and 100 c/sec. These were randomized for each presentation of the series.

Following the experiment the animal was sacrificed with Nembutal and the brain perfused with saline and formaldehyde. The brain was sectioned and the extent of the lesion determined grossly and by selected sections stained with hematoxylin and eosin. All lesions were shown to be confined to the cortex and immediate subcortical white fibers. In no instance were thalamic structures damaged.

OBSERVATIONS

The paroxysmal focus

The cortical penicillin injection resulted in an orderly sequence of events. Characteristically within several minutes after the injection high amplitude (200-500 μV.) spikes appeared at the area of injection (fig. 1). These at first were seen irregularly every 10-15 sec. They then gradually increased in number so that 1-4 occurred spontaneously during a 10 sec. interval. These focal spikes could be readily evoked by photic stimulation.

This stage of spiking might persist several hours without change. Usually, however, within 15-20 min., short periods of photic stimulation at certain frequencies resulted in the appearance of multiple fast spikes (10-20 c/sec., 100-300 μV.) which continued several hours, the convulsions occurred at approximately 4 to 6 min. intervals and lasted from 2 to 4 min., followed by a period of cortical silence out of which arose the focal slow spike. Thus the sequence, focal intermittent slow spiking, focal multiple fast spiking, gradual

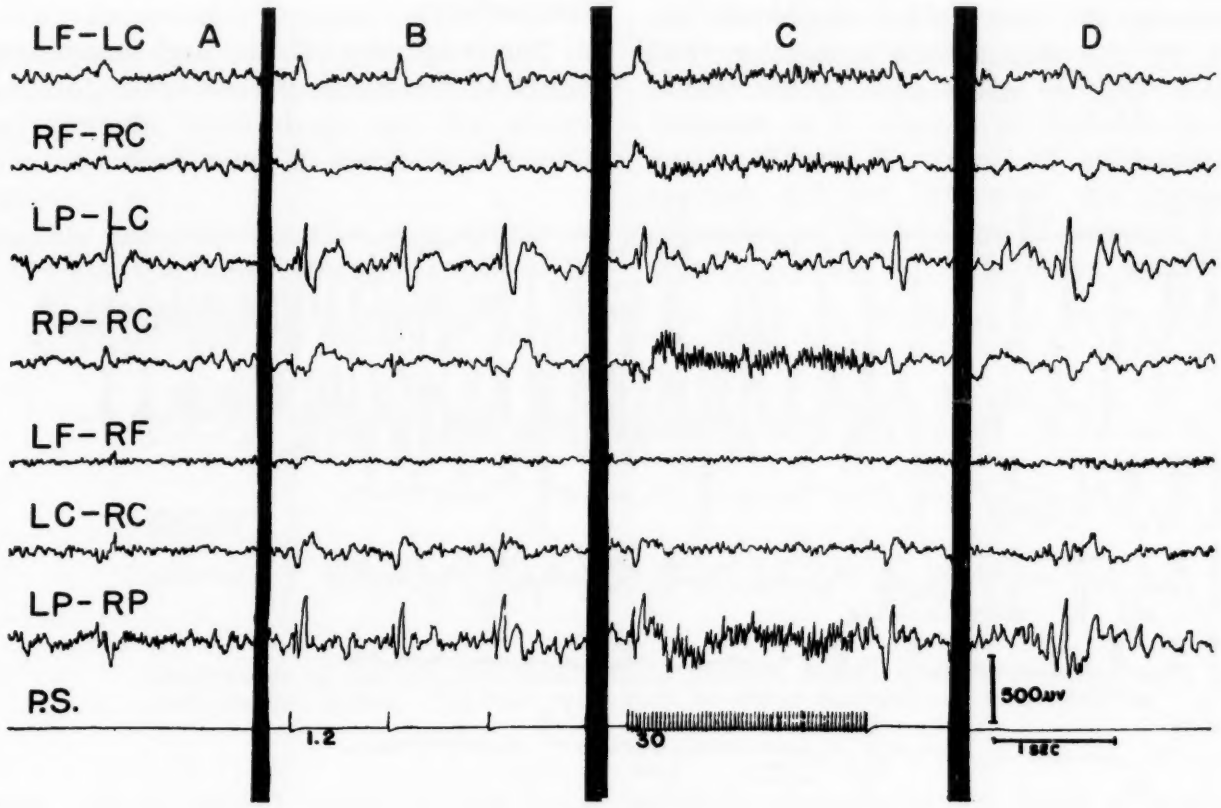


Fig. 1
Cat # 20. Curarized.

A. Focal slow spike arising spontaneously from the left visual area 2 min. following the local injection of penicillin in oil.

B. Evocation of the slow spike with each flash at 1.2 c/sec. Record of photic stimulus (P. S.) bottom line.

C. Response to a short presentation at 30 c/sec. Note lack of normal "following" posteriorly on side of lesion.

D. Spontaneous slow spike 2 h. following initial injection. Note particularly increased amplitude of the slow spike with increased duration of the spike complex. Designation of electrode combinations in this and subsequent figures. L — left, R — right, F — frontal, C — central, P — posterior.

seconds after the end of the stimulation (fig. 2, B and C).

This paroxysmal after-discharge in the non-curarized preparation at first was not accompanied by motor manifestations. Later these after-discharges increased in length and spread both anteriorly and contralaterally and were accompanied by convulsions. The convulsions showed a typical Jacksonian spread. In most preparations after several spread of the multiple fast spike discharge to generalized involvement followed by cortical silence, is characteristic of the pathophysiologic lesion induced by the penicillin in oil preparation. However, there was a gradual change in the frequency of occurrence and length of the spontaneous discharges over a period of several hours. There were also gradual changes in the character of the slow spike complex during the course

of the experiment. These were: 1, increased amplitude, 2, increased duration, and 3, increased spread (fig. 1, D). Successive spikes occasionally varied slightly in form and amplitude.

The focal slow spikes and the multiple fast spikes were clearly distinguishable. The slow spikes could be evoked by photic stimulation whereas the fast spikes appeared unaffected by the stimulation once they had developed. One or more slow spikes, either spontaneous or evoked, always immediately preceded the multiple fast spike discharge (fig. 3). At the onset of the multiple fast spikes there was usually reduction in overall amplitude of the discharge. The slow spikes remained localized to the area of injection and were without apparent associated peripheral manifestations. The multiple fast spikes, in contrast, spread to other areas and when the spread reached motor centers, a tonic seizure occurred. This later progressed to a clonic stage, the EEG showing brief discharges of multiple spikes alternating with slow waves. Because of the association of the multiple fast spikes with convulsive manifestations in the non-curarized preparation, these are subsequently referred to as *seizure discharges.*

The response of the slow spike to photic stimulation

The response of the high amplitude irregularly discharging slow spike to intermittent photic stimulation could be studied when the fast repetitive spiking was not present. These spikes could be elicited as 1:1 responses with slow (½-3 c/sec.) stimuli (fig. 1, B). With faster stimuli several phenomena were noted. One was that the spike would respond typically only to every other flash in the 4-7 c/sec. range, and to every third flash in the 7-10 c/sec. range. Occasionally, to still faster stimuli, the response could be correlated with every 4th, 5th or even 6th flash. The spikes tended to respond in the 2-3 c/sec. range ir-

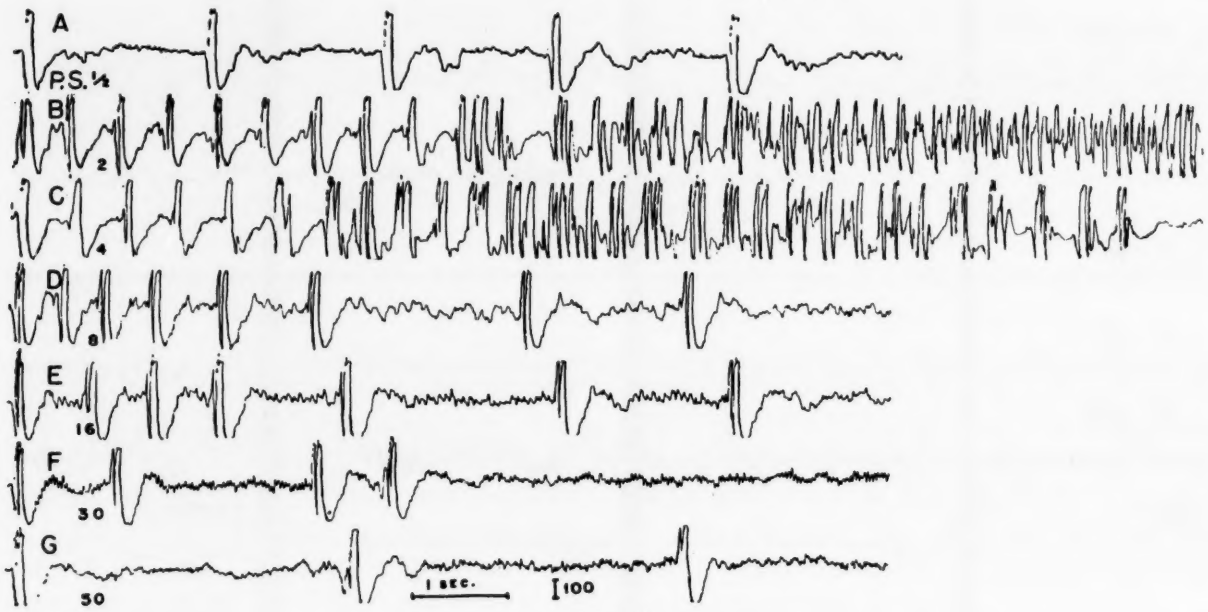


Fig. 2

Cat # 33. Curarized. Representative samples of the response of the focal slow spike to photic stimulation at various frequencies. Photic stimulus presented throughout 10 sec. of cut-out. Sample extended in B and C to demonstrate persistence of seizure activity after cessation of stimulus. Record of photic stimulus not included. LC — LP in all samples.

A. 1:1 response at ½ c/sec.
B. 1:1 response initially at 2 c/sec. with precipitation of self-sustaining seizure discharge.
C. 1:2 response initially at 4 c/sec. with precipitation of self-sustaining seizure discharge.
D, E, F, G. Progressive decrease in number of slow spikes during stimulation at 8, 16, 30 and 50 c/sec.

respective of the frequency of photic stimulation. These were the usual responses. However, instances were noted in which an alternate response occurred to a flash rate as low as 1 c/sec. and a 1:1 response to as high as 7 c/sec. Many different frequency patterns of response were seen. For instance, alternating 2nd and 3rd subharmonic responses occurred. In another instance the response dropped out to every 3rd flash. At times, the evoked single responses might continue for several seconds, then drop out for several seconds, and then come in again in a regular sequence.

Another phenomenon that was clearly related to flash frequency was the *length* of the response. At ½ and 1 c/sec. it was usual for the response to occur without change indefinitely provided a seizure discharge did not intervene. With progressively faster stimuli the total discharge length gradually decreased until only a single spike was evoked at the onset of the stimulus. The frequency at which this occurred varied somewhat but it was frequently seen at 30 c/sec. and above. "Off" responses were usual also at these frequencies (fig. 1, C). A characteristic pattern of spike discharge to rapid stimulation was several slow spikes occurring at short intervals (2-3/sec.) followed by several at increasingly longer intervals (fig. 2). Single slow spikes seen only at the initiation of the stimulus were progressively less frequently observed in the slower frequency range but were noted as low as 1 c/sec. Termination of the response to slow stimuli usually occurred with subharmonic responses at increasing intervals. However, instances were observed where a 1:1 response continued but with gradually decreasing amplitude.

In addition to the observations relating to the frequency and pattern of the spike responses, variations could be observed in the *form* of the spike with changing stimulus frequency. It is of interest that the frequencies that evoked the spikes for indefinitely long periods (½ and 1 c/sec.) were also those that gave a spike response whose form did not change during the period of observation. The response to 2 c/sec. was variable in this regard. Above 3 c/sec., if subharmonic responses did not intervene, an apparent reorganization of the form of response appeared inevitable (fig. 4). The wave form and amplitude changes varied from preparation to preparation, but were relatively constant for any given preparation. An expected and not infrequent finding was that of lower amplitude of 1:1 responses above 3 c/sec. However, in some instances the fast (4-7 c/sec.) 1:1 responses appeared of higher amplitude. In some cases this appeared to be due to the superimposition of the spike of each successive response on the negative swing of the slow wave of the preceding wave complex. In this range, it was common to see slight modifications of the form of the response with each successive stimulus. Differences from preparation to preparation may be in part explained on the basis of electrode placement and location of the discharging focus in relation to the electrodes.

These observations suggest the difficulty in designating the refractory period of the neural system responding with the spike discharge. If one takes the highest frequency

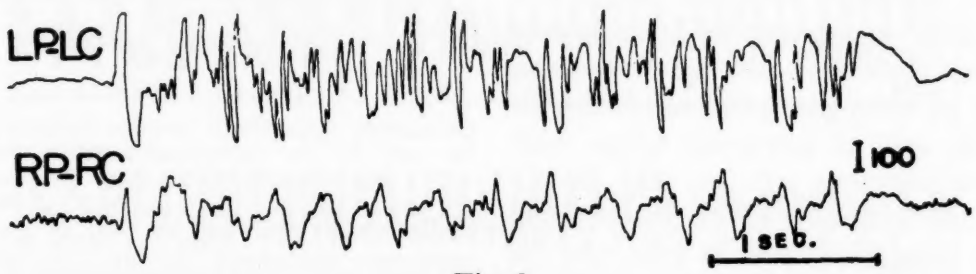


Fig. 3

Illustration of the constant relationship between the slow spike and the multiple fast spikes. The slow spike may be either spontaneous or evoked.

at which a 1:1 response usually occurs the refractory period would be in the order of 330 msec. However, the instances in which a response occurs to every other flash at a 1 c/sec. flash rate indicates that the system may be refractory for longer than 1000 msec. Two other observations suggest that even though the system will respond in a 1:1 manner at frequencies of 3 c/sec. (and occasionally higher) that complete recovery does not occur in intervals shorter than 330 msec. an autonomous firing of rapid spikes, this firing usually being at rates between 10-20 c/sec. These seizure discharges were always seen to arise from the region of the slow spike focus and progress gradually to involve adjacent homolateral and contralateral electrodes.

In some experiments, pairs of frequencies were compared for their tendency to bring on such seizure discharges. In one experiment flash rates of 3 c/sec. and 30 c/sec. were

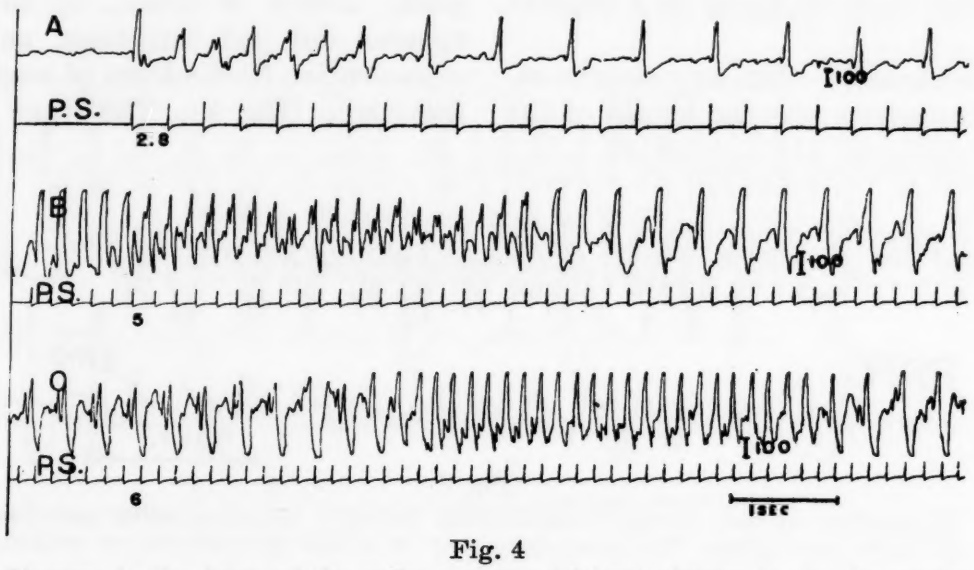


Fig. 4

Changes in the form of the spike response without change in the frequency of the photic stimulus.

A. Increased amplitude with conversion of a 1:1 to a 1:2 response with stimulation at 2.8 c/sec. Preparation anesthetized with Nembutal.

B. Progressive change in the response configuration during 1:1 "following" with a stable pattern appearing after a 1:2 relationship is established. Preparation curarized.

C. Alteration of the response characteristics with a change from a 1:2 to a 1:1 relationship. Preparation curarized.

These observations are that at 3 c/sec. and above in no instance has the discharge continued indefinitely, whereas this does occur at slower rates, and that modifications in the form of the response occur.

The slow spikes were not evoked by auditory or somesthetic stimuli, in the preparations with visual cortex injections. In other preparations injection of penicillin in auditory cortex resulted in discharges responsive exclusively to auditory stimuli.

The multiple fast spike discharge

As previously indicated, as the experiment progressed certain frequencies would induce presented for 10 sec. each with an interval of 30 sec. between stimulations. Each frequency was presented sequentially twice to a total of 80 samples. Paroxysmal after-discharge lasting one or more seconds after the termination of the stimulus occurred 29 times to the 3 c/sec. flash rate compared with only once to the 30 c/sec. rate. Spontaneous seizure discharges occurred twice in the intervals after the 3 c/sec. stimulations and 5 times after the 30 c/sec. Other early experiments showed that 10-20 c/sec. flash rates were not as effective as slower frequencies and that frequencies above 20 c/sec. were minimally effective.

After the general trend was established, a series of 7 cats was used to define more clearly the relative effectiveness of each of 22 frequencies in inducing rapid paroxysmal discharges. The frequencies were randomized and presented for 10 sec. followed by a 20 sec.

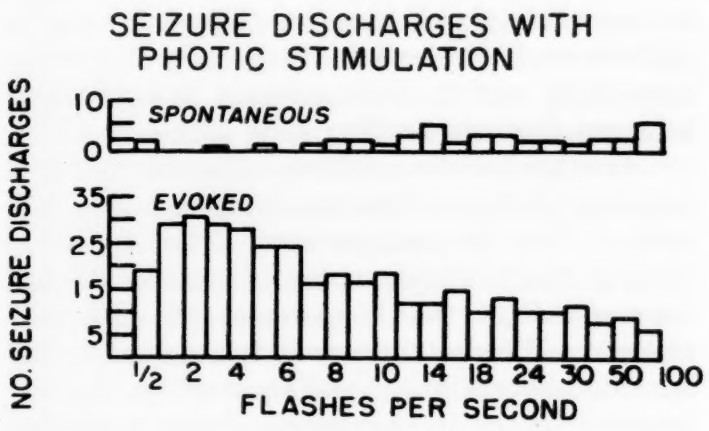


Fig. 5

The number of evoked seizure discharges persisting more than 1 sec. after termination of 10 sec. of photic stimulation for each of 22 frequencies. Frequencies sampled: ½, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 21, 24, 27, 30, 40, 50, 100. Total trials at each frequency, 35. Seizure discharges occurring spontaneously between presentations are also graphed. See text for further explanation.

period after the end of the stimulus or seizure discharge prior to the presentation of the next frequency. The cats were curarized and artificially respirated. Thirty-five trials at each frequency were obtained, the number for each cat varying from 3 to 10. Of the total of 757 trials, 364 seizure discharges occurred. The number of positive responses at each of the 22 frequencies is shown in figure 5. As shown, frequencies from 1-4 c/sec. gave the highest number of positive responses. The number gradually fell off for higher frequencies so that above 24 c/sec. less than one-third of the presentations resulted in seizure discharge. None of the preparations showed an emphasis in other than the low frequency range. This was also true of other non-curarized alert preparations in which the injection of penicillin was carried out under local anesthesia.

The number of positive responses during any given series of the 22 stimulus frequencies varied from 2 to 20. When only 2 or 3 frequencies evoked seizure activity, the active frequencies were almost invariably in the slow range. As the number of after-discharges increased, higher frequencies were progressively brought in as activating frequencies. This great variation in responsiveness of the focus from preparation to preparation as well as in time in any given preparation should be noted. Early in the experiment without exception, and rarely throughout the entire experiment in certain preparations, no after-discharge would occur to any frequency, although the slow spikes could be readily evoked. At the other extreme seizure activity would occur at the initiation of any frequency. At this point the serial presentation of stimuli was routinely discontinued for no differential effect could be observed. The increasing excitability of the focus with time is demonstrated by the fact that immediate onset of seizure activity preceded by a single evoked slow spike occurred to less than 1 per cent (1 of 142) of the presentations during the first series, 11 per cent of the second series, 27 per cent of the third, and 40 per cent of the fourth. This type of onset occurred 117 times in this series. The remainder began at varying times following the initiation of the photic stimulus.

Data obtained on other alert preparations in which the photic stimulus was continued throughout complete seizure cycles, demonstrated that 1-4 c/sec. stimuli were also clearly more effective in causing an early onset of seizure discharge than either slower or faster frequencies.

A total of 40 seizure discharges were observed to arise during the 20 sec. intervals between presentations of the photic stimulus. These spontaneous discharges tended to occur after periods of stimulation with frequencies less effective in initiating seizure discharges. Thus only one such discharge occurred after the trials with 1, 2, 3 and 4 c/sec. stimuli whereas 11 occurred after 30, 40, 50 and 100 c/sec. stimulation. An average of the spontaneously occurring seizures cannot be taken as a baseline of seizure activity inasmuch as the repeated stimulations may well trigger discharges on the verge of occurring spontaneously. Furthermore, it is not known

whether or not there is an actual increase in the number of seizures as a result of the repeated stimulations or merely a redistribution of the seizures by the differential action of the various frequencies.

Figure 6 shows the incidence of slow spike discharges in periods of non-seizure pattern during the 35 presentations of the 22 stimulus frequencies and spontaneous spikes in the

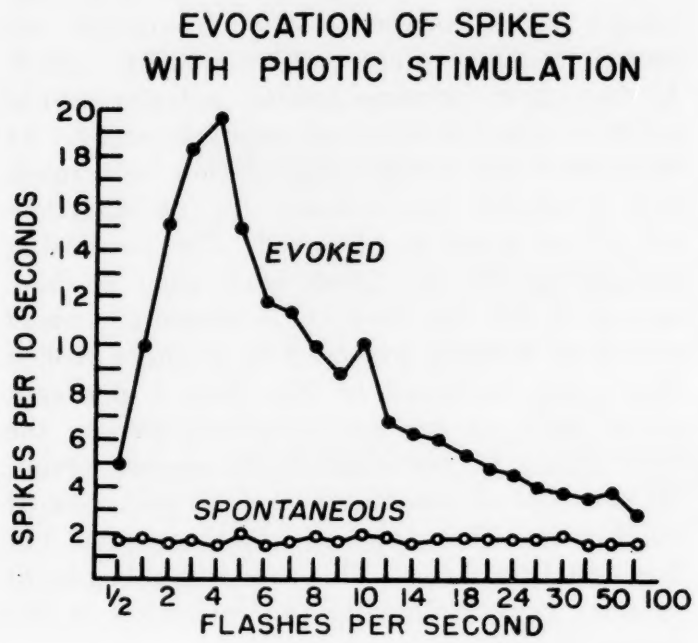


Fig. 6

Two curves showing the incidence of evoked slow spikes correlated with frequency of the photic stimulus and the incidence of spontaneous spikes occurring in the 10 sec. prior to each presentation. The same frequencies are sampled as in figure 5. See text.

10 sec. period prior to each presentation. The curve for spontaneous spikes serves as a control as to the variability of their incidence. The average consistently fell between 1.5 and 2.0 spikes per 10 sec. The incidence of evoked spikes is given in average number of spikes per 10 sec. of stimulus duration. Instances where only a single spike immediately followed by a seizure discharge occurred were omitted from the tabulation.

It is seen that there is an increasing effectiveness of the stimulus to 3 and 4 c/sec. with a gradually decreasing effectiveness to 100 c/sec. It is of interest that the slow spike incidence for 100 c/sec. is little more than one over the spontaneous level, suggesting that the "on" spike at the initiation of the stimulus can alone account for the slightly increased incidence. Suppression below the spontaneous level was not seen with any of the tested frequencies. This curve is similar though not identical to the curve of the number of seizure discharges occurring during each frequency, suggesting a relationship between the two phenomena. The most notable difference is the relatively greater effectiveness of ½ and 1 c/sec. stimuli in activating seizures than in evoking slow spikes.

Another distinguishing feature is now apparent between the slow and multiple fast spikes. The frequencies most effective in inducing the multiple spike discharge do not correspond to the frequencies of such discharges, whereas the critical frequencies for maximal evocation of the slow spikes do correspond to the upper range of the repetition rate of the slow spike.

The curve for slow spike incidence has several inherent defects which should be mentioned. One results because a time period must be chosen. The results will vary according to the length of this period. Thus, as previously mentioned, responses at very slow frequencies — ½, 1, 2 c/sec. — will continue for long periods of time unchanged, whereas responses at high frequencies occur grouped in the first several seconds. With time periods longer than 10 sec. the very slow frequencies will give relatively higher values. Another defect is that the seizure discharge intervenes more often with slow frequencies so that the initial 2-3 sec. must be accepted as the typical response for the entire 10 sec. Furthermore, such a curve tells nothing of the form of the spike. In spite of these limitations it is felt that the parellelism is worthy of note.

DISCUSSION

Clinical observations suggest that frequencies higher than the ones found in this experimental study are most effective in inducing seizure discharges, and that harmonic relationships are important. Walter and Walter (1949) state that in patients, mostly children, whose spontaneous spike-and-wave seizure discharges arise or are most prominent in the posterior regions, flash rates at the fourth or fifth harmonic of the fundamental wave and

spike rhythm are most effective. These are in the 12 to 18 c/sec. range. In rare cases the seizure pattern can be induced by stimulation at the fundamental. Storm von Leeuwen (1953) cites a case in which the only way to provoke an EEG abnormality was to flicker at 18-20 c/sec. A major seizure followed in this instance. He goes on to state: "The effective flash frequency usually is about 15 per sec. but is sometimes lower." Gastaut *et al.* (1951) have also emphasized the particular efficacy of 15 c/sec. Thus the emphasis of the 1-4 c/sec. frequencies in evoking seizures in these preparations stands in sharp contrast to the clinical observations. It may be that species differences are such that further speculation is unwarranted. However, in the event that this is not the case, the difference in the type of basic pathophysiologic disturbance should also be considered. Our lesion is induced by a chemical agent and the neural abnormalities may be quite different from those present in either a traumatic scar or in the physiologic defect in "idiopathic" seizures. The cited cases demonstrate bilaterally synchronous spike-and-wave responses and presumably fall into the "idiopathic" group. The location of the epileptogenic disturbance may also play a role. Thus our lesion is centered within visual cortex whereas the disturbance in "idiopathic" epilepsy may be diffuse or may particularly involve deep midline nuclei. This concept may be extended to include the possibility that the photic stimulus can directly influence the epileptogenic focus in our preparations whereas in the usual case of photogenic epilepsy the effect may be mediated through the influence of the stimulus on the normal rhythms.

Gastaut *et al.* (1951) have carefully investigated the normal cortical excitability cycle in the cat and have proposed that this is the explanation of the effectiveness of the 15 c/sec. stimulus frequency. Obviously, this suggestion is not applicable to our findings. A more pertinent observation may be that of Gastaut and Hunter (1950) that the strychninized cortex has a refractory period of 250 to 350 msec. In preparations using local cortical application of strychnine or Metrazol, they also noted "alternance" of response to stimuli faster than those corresponding to the refractory period, the phenomenon of a single initial response to "sufficiently high" frequencies, the appearance of spontaneous spikes not showing a precise relationship to the stimulating rhythm at these high frequencies and the fact that the local application of a convulsant agent to the visual cortex never brings about the irradiation of the response to light to the anterior brain regions. Cobb *et al.* (1955) have recently described characteristics of photically evoked strychnine spikes in cats under Nembutal anesthesia. They noted that the maximum frequency at which the spikes could be evoked was between 3 and 3.5 c/sec., that the response occurred at subharmonics of the flash frequency with stimulation between 4 and 9 c/sec., and that at higher frequencies the spikes were either completely blocked or else occurred spontaneously with no relation to the flashes. Thus many aspects of the form and behavior of the penicillin evoked slow spikes to intermittent photic stimulation appear similar to the strychnine and Metrazol spikes.

In describing the characteristics of cortical irradiation potentials induced by Metrazol and photic stimulation in cats under Nembutal anesthesia, Hunter and Ingvar (1955) noted that at a stage when spontaneous trains of 3 c/sec. spike and waves were present, stimulation with "2.5 to 4 flashes per sec." resulted in either a generalized seizure or an "attenuation" and disappearance of the irradiation response. There is a close resemblance between these findings and those seen with the cortical injection of penicillin. The main difference appears to be that in the latter situation the seizure can be observed to develop by gradual spread from the focal spike discharge, "irradiation" not occurring. "Attenuation" was seen repeatedly in the present study. It was more likely to follow in the early phase of the focal abnormality where it was established that the length of the response was related to the frequency of stimulation. Later, seizure activity almost always occurred with stimulation at critical frequencies. It is interesting to note that Hunter and Ingvar concluded that the fre-

quency sensitivity was dependent upon cortical factors. It is reasonable to presume this to be true also in the present study.

The refractory period of the neural system responding after the local application of penicillin as evidenced by the point of alternation of response may be between 250 and 350 msec., although some evidence suggests complete recovery occurs more slowly. However, in general those frequencies whose intervals approximate the refractory period of the discharging system give both the greatest number of slow spikes and seizure discharges. Frequencies that are subharmonics or harmonics of the frequency that corresponds to the refractory period have a lesser tendency to evoke seizure discharge. In none of our preparations was there evidence of any one harmonically related group of frequencies being particularly effective.

As the photic stimulus becomes slower it reaches the point of evoking the slow spikes at the same rate as the spontaneous slow spikes (1-2 per 10 sec.). The spikes are thus rearranged but there is no observable increase in the propensity of the focus to induce a seizure discharge. This tendency increases with increasing incidence of the slow spikes, with the frequencies that group around the refractory period being of greatest effectiveness in precipitating seizure discharges. Above 5-6 c/sec. the decreasing incidence of seizures closely parallels the decreasing ability of the higher frequencies to induce slow spikes. The decreased amount of slow spike activity on the two slopes of the curve is clearly the result of different mechanisms, the mechanism being apparent for the up slope and obscure for the down slope, even though the fact that most of the rapid frequencies will fall within the refractory period is clear. Somehow, however, the excitability of the system is reduced during the continued rapid stimulation so that even those stimuli that would be expected to fall during the excitable portion of the period fail to fire the system.

The behavior of the slow spike under different frequencies of photic stimulation appears to serve as an indicator of which frequencies will precipitate actual seizure discharges most frequently. Whether or not certain patterns of slow spike behavior are causally related to the seizure discharge is a matter for speculation. The constant sequential relationship between the slow spike and seizure discharges, as well as the correlation between the relative ability of various frequencies to provoke both slow spikes and seizure discharges, leads to the consideration of such a possibility. An alternate possibility is that the slow spike and the multiple fast spiking are both controlled by a common neural mechanism.

Another question of some interest concerns the relationship between certain components of the normal response of the visual cortex to a single flash and the initiation of the paroxysm. The complex electrical events following a visual stimulus have been outlined by Brazier (1953). Two components appear to be of particular interest, the primary response, a short latency potential of restricted spread, and the secondary discharge, a longer latency potential, of wider distribution. Whether the primary response or the secondary discharge is of exclusive efficacy in the evocation of the paroxysmal slow spikes and the seizure discharges cannot be answered from our data. However, it appears that frequency rates which might be expected to allow only repetition of the primary response are less effective than those which would allow both a primary response and secondary discharge to follow each stimulus.

CONCLUSIONS

1. The sequence of events resulting from the local cortical injection of penicillin in oil is described. With visual area lesions, the focal intermittent slow spikes are responsive to intermittent photic stimuli and can be distinguished from the multiple fast spikes which are non-responsive. The latter are manifested by seizures, if spread to motor centers occurs.

2. Variations in the frequency of afferent visual stimuli affect both the incidence of the slow spike and seizure discharges. In the present study, slow frequencies (1-4 c/sec.) are observed to give a maximal incidence of regular slow spikes over long periods of time and a high incidence of seizure discharges. Fast frequencies result in irregular subhar-

monic responses for brief periods or single slow spikes and precipitate seizures infrequently.

3. The effective frequency range corresponds with frequency response characteristics of the slow spike rather than with either the frequency range of the normal alert cat electroencephalogram or of the multiple fast spikes.

REFERENCES

BORKOWSKI, W. J. and FORSTER, F. M. Convulsant effects of penicillin on the cerebral cortex. *J. Neuropath. Exp. Neurol.*, **1947**, *6*: 201-205.

BRAZIER, M. A. B. A review of physiological mechanisms of the visual system in relation to activating techniques in electroencephalography. *Third Int. Congress EEG Clin. Neurophysiol., Suppl. No 4*, **1953**, 93-107.

CLEMENTI, A. Strychninizazzione della sfera corticale visiva ed epilessia sperimentale da stimoli luminosi. *Arch. fisiol.*, **1929**, *27*: 356-387.

COBB, S. Photic driving as a cause of clinical seizures in epileptic patients. *Arch. Neurol. Psychiat.*, Chicago, **1947**, *58*: 70-71.

COBB, W. A., COWAN, W. M., POWELL, T. P. S. and WRIGHT, M. K. The relation between photically evoked specific responses and strychnine spikes in the visual cortex of the cat. *J. Physiol.*, **1955**, *129*: 305-315.

FAETH, W. H., WALKER, A. E. and ANDY, O. J. The propagation of cortical and subcortical epileptic discharge. *Epilepsia*, **1954**, *3*: 37-48.

GASTAUT, H., GASTAUT, Y., ROGER, A., CORRIOL, J. et NAGUET, R. Etude électrographique du cycle d'excitabilité cortical. *EEG Clin. Neurophysiol.*, **1951**, *3*: 401-428.

GASTAUT, H. and HUNTER, J. An experimental study of the mechanism of photic activation in idiopathic epilepsy. *EEG Clin. Neurophysiol.*, **1950**, *2*: 263-287.

GOWERS, W. R. *Epilepsy and other chronic convulsive diseases: Their cause, symptoms and treatment.* New York, William Wood and Company, **1881**, 255 pp.

GOZZANO, M. Ricerche sui fenomeni elettrici della corteccia cerebrale. *Riv. Neurol.*, **1935**, *8*: 212-261.

HUNTER, J. and INGVAR, D. H. Pathways mediating Metrazol induced irradiation of visual impulses. *EEG Clin. Neurophysiol.*, **1955**, *7*: 39-60.

MARSHALL, C., WALKER, A. E. and LIVINGSTON, S. Photogenic epilepsy: parameters of activation. *Arch. Neurol. Psychiat.*, Chicago, **1953**, *69*: 760-765.

MORUZZI, G. General mechanisms of seizure discharges. *Third Int. Congress EEG Clin. Neurophysiol., Suppl. No. 4*, **1953**, 221-232.

SCHWAB, R. S. and ABBOTT, J. A. The clinical value of photic Metrazol activation technique. *EEG Clin. Neurophysiol.*, **1951**, *3*: 378.

STORM VON LEEUWEN, W. and KOK, L. Some ways in which EEG changes may be produced by photic stimulation. *Folia Psychiat. Neurol. Neurochir. Neerl.*, **1953**, *56*: 519-524.

TERZIAN, H. e TERZUOLO, C. Ricerche elettrofisiologiche sull' epilessia fotica di Clementi. *Arch. fisiol.*, **1952**, *51*: 301-320.

VAN BUSKIRK, C., CASBY, J. U., PASSOUANT, P. and SCHWAB, R. S. The effect of different modalities of light on the activation of the EEG. *EEG Clin. Neurophysiol.*, **1952**, *4*: 244-245.

WALKER, A. E. and JOHNSON, H. C. Convulsive factor in commercial penicillin. *Arch. Surg.*, **1945**, *50*: 69-73.

WALTER, V. J. and WALTER, W. GREY. The central effects of rhythmic sensory stimulation. *EEG Clin. Neurophysiol.*, **1949**, *1*: 57-86.

WALTER, W. G., DOVEY, V. J. and SHIPTON, H. W. Analysis of the electrical response of the human cortex to photic stimulation. *Nature*, **1946**, *158*: 540-541.

Reference: KOOI, K. A. and BECK, E. C. Frequency of photic stimulation as a variable in the activation of experimental convulsions. *EEG Clin. Neurophysiol.*, **1956**, *8*: 653-663.

ANNOUNCEMENTS

ARNMD MEETING

The Annual Meeting of the Association for Research in Nervous and Mental Disease will be held on December 7 and 8, 1956 at the Hotel Roosevelt, New York City. The subject of the meeting will be "The Brain and Human Behavior".

AMERICAN PSYCHOSOMATIC SOCIETY MEETING

The American Psychosomatic Society will hold its Fourteenth Annual Meeting at Chalfonte-Haddon Hall in Atlantic City on Saturday and Sunday, May 4 and 5, 1957.

The Program Committee would like to receive titles and abstracts of papers for consideration for the program no later than December 1, 1956. The time allotted for presentation of each paper will be twenty minutes.

Abstracts, in sextuplicate, should be submitted for the Program Committee's consideration to the Chairman, at 551 Madison Avenue, New York 22, New York.

CLINICAL AND LABORATORY NOTES

Editor for Western Hemisphere and Far East, R. S. SCHWAB, M.D., Boston, U.S.A.
Editor for Europe and Middle East, F. BUCHTHAL, M.D., Copenhagen, Denmark

UNUSUAL EEG IN UNCONSCIOUS PATIENT WITH BRAIN STEM ATROPHY

ARNE LUNDERVOLD, M.D., TORMOD HAUGE, M.D. and AAGOT C. LÖKEN, M.D.
Department of Neurology, Department of Neurosurgery and the Neuropathological Section of the Institute of Pathologic Anatomy, Oslo University, Oslo, Norway

(Received for publication : April 26, 1956)

Electroencephalographic changes in disturbances of consciousness have already been reported by Berger (1932). The same observation has later been confirmed by numerous authors (Strauss, Ostow and Greenstein 1952; B. Kaada 1952).

The following case of a patient who, subsequent to vertebral angiography, stayed unconscious for one year and a half without appreciable EEG changes, exhibits many points of interest.

Case report: A. F., male, age 63 was admitted to the Neurosurgical Department of the University Hospitals in Oslo with clinical signs indicating bulbar lesion.

To conform the diagnosis which was vascular

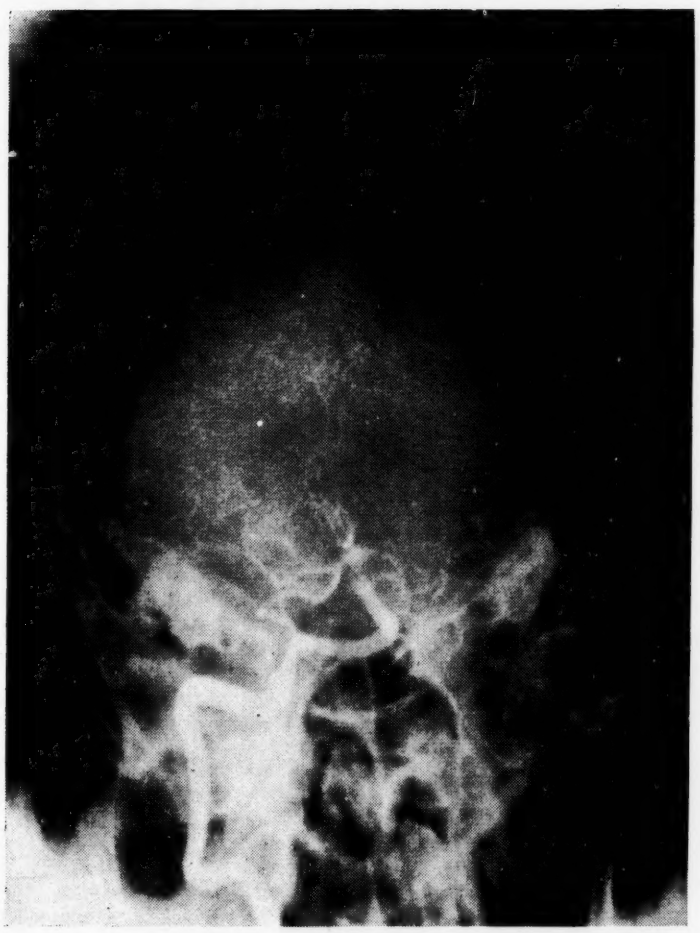


Fig. 1
Vertebral arteriogram. Contrast-filling of the arteries of the brain stem area to the level of the superior cerebellar arteries.

Fig. 2
Base of brain showing extensive arteriosclerosis and organized saccular aneurysm at the top of basilar artery obstructing the passage of contrast from the basilar to the posterior cerebral arteries and thus explaining the non-filling of these arteries in the arteriogram.

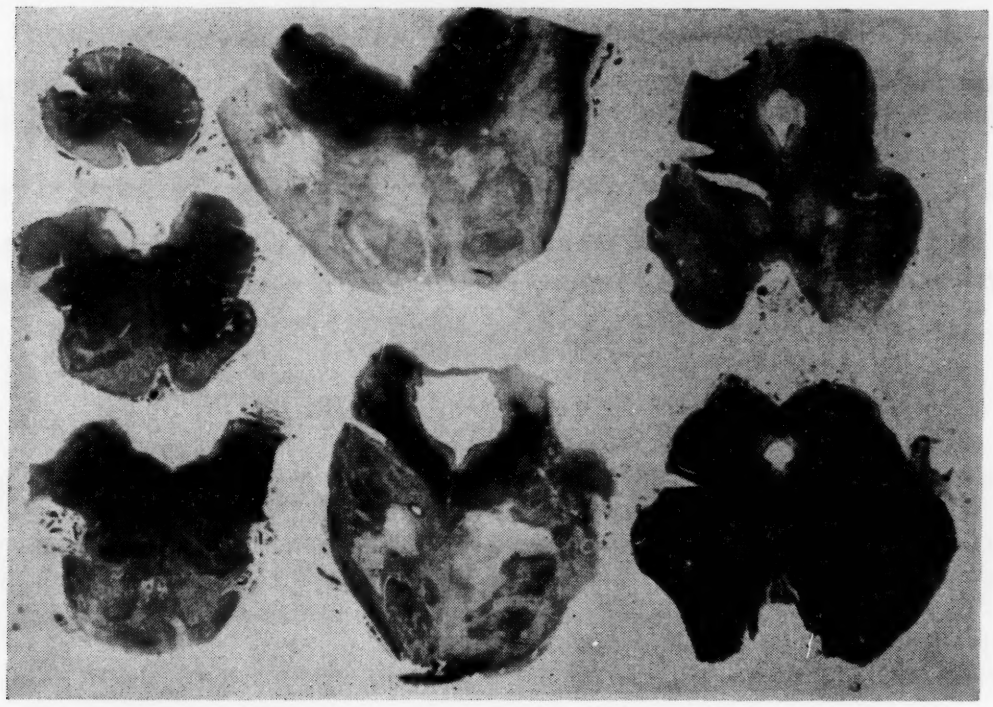


Fig. 3
Sections (Weil's myeline stain) at level of medulla oblongata, showing bilateral atrophy of pyramidal tracts, posterior fascicules, median lemniscs, cerebellar tracts, whole pontine region with posterior part of mesencephalon including inferior colliculus.

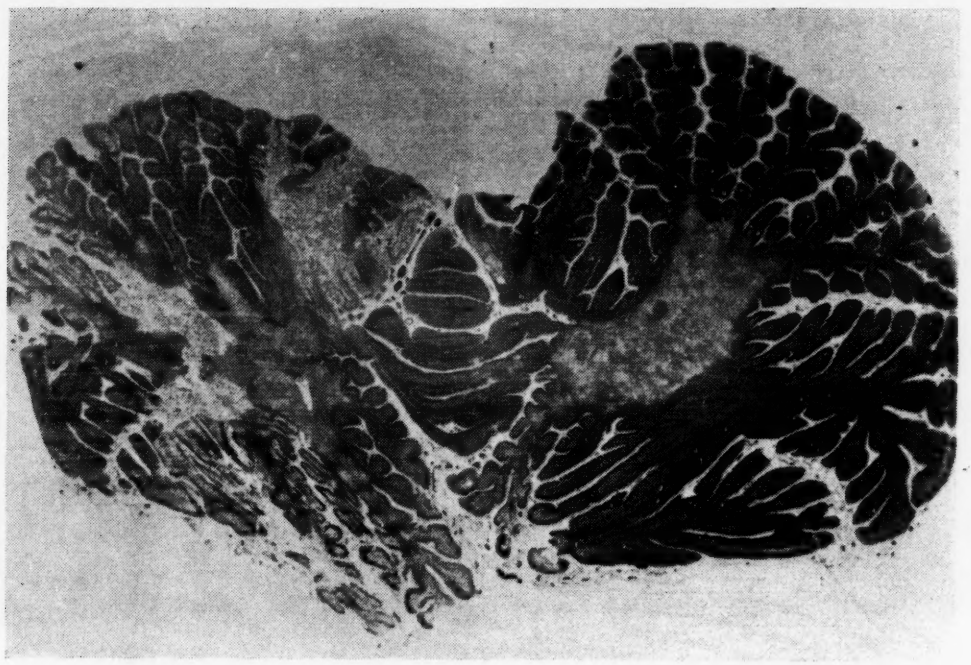


Fig. 4
Sections (Weil's myeline stain) of the cerebellar cortex showing it for the most part destroyed.

lesion of the brain stem, an injection of 6 ml. Thorotrast was made in the right vertebral artery with the catheter methode.

Three minutes after the injection a pronounced aggravation of his bulbar signs were evident and the patient became unconscious. Tracheotomy was performed immediately.

The main clinical findings were as follows: the pupillary reaction to light was preserved. The corneal reflexes were weakened. There was no response to pain stimuli, neither from face nor from rest of body. There was hypotonic quadriplegia, and after

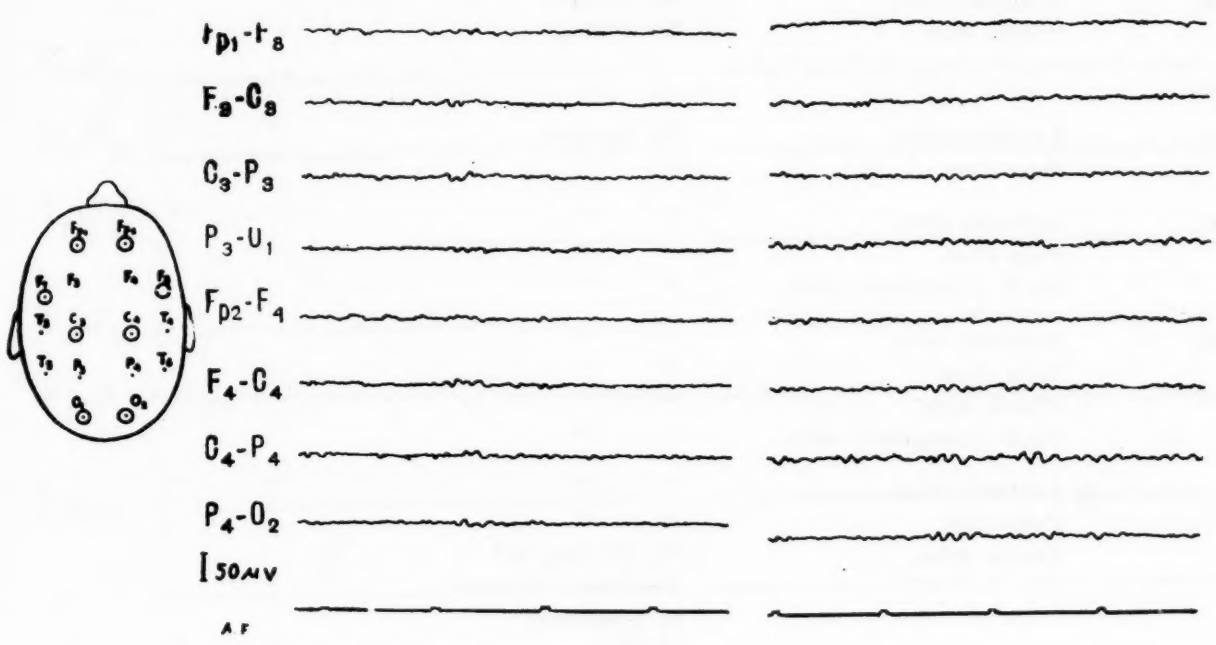


Fig. 5

In all registrations the electrodes are placed as in this figure and the time marker shows every second.
Left. EEG registered 2 days before the patient became unconscious.
Right. EEG registered the day after the patient became unconscious.

some weeks loss of plantar reflexes — and all deep reflexes. The arteriogram (fig. 1) showed contrast filling of the arteries of the brain stem, including the superior cerebellar arteries, but not of the posterior cerebral arteries.

The patient's clinical condition remained unchanged for one year and a half, when he suddenly succumbed to coronary thrombosis.

The autopsy revealed extensive arteriosclerosis of the vertebral arterial system and an obliterated saccular aneurysm at the top of the basilar artery (fig. 2) obstructing the passage of water from the basilar to the posterior cerebral arteries and thus explaining the non filling with contrast of these arteries in the arteriogram. On microscopic examination the cerebral cortex appeared normal. In the subcortical and deeper white matter the rather wide perivascular spaces and the densely packed glial cells indicated some diffuse atrophy. The basal ganglia appeared normal but for a marked precipitation of ferrocalcium in the walls of the arteries, veins and capillaries of the globus pallidus. The hypothalamic nuclei appeared normal. The lower parts of the red nuclei were deprived of nerve cells, while the rostral parts were preserved. The substantia nigra had lost a few nerve cells. The superior colliculi and the lateral geniculate bodies exhibited no pathological changes, while the medial geniculate bodies appeared reduced in size. The pontine region including its reticular substance was severely damaged and mostly replaced by a spongy glial tissue. The nuclei of the sixth, seventh and eight cranial nerves could not be found, while the third and fourth were more or less preserved. The pyramidal tracts were destroyed except for a few myelinated fibres in the brachia conjunctiva (fig. 3).

The cerebellar cortex, the dentate nuclei and the roof nuclei were for the most part destroyed (fig. 4).

During the patient's stay in hospital 17 EEG recordings were made, 2 of which before the vertebral angiography. The recordings were made under standard conditions and after the application of various activating stimuli, such as light, touch, pain and smell stimuli. Recordings were also made during sleep.

TABLE I

Date	Activation		Results
1953			
Nov. 4			Slight depression of the electrical activity in the left temporal and parietal region. 8/sec. alpha activity.
Des. 2			
Des. 4 a.m.	Immediately after the injection of Thorotrast into the right vertebral artery with the patient unconscious.		Normal 8/sec. alpha activity.
Des. 4 p.m.	Acoustic stim. Photic stim.	No changes No driving	" " " "
Des. 5 a.m.			" " " "
Des. 5 p.m.	Acoustic stim. Pain stim.	No changes " "	" " " "
Des. 6 a.m.	Acoustic stim. Pain stim. Smell (camphor) stim.	" " " " " "	" " " "
Des. 6 p.m.	Acoustic stim. Pain stim. Photic stim. Smell (camphor) stim.	" " " " " " " "	" " " "
Des. 9	Acoustic stim. Pain stim. Photic stim.	" " " " No driving but sometimes changes in frequency	" " " "
Des. 11			" " " "
Des. 14	Sleep stim.		" " " "
Des. 15	Sleep stim. Acoustic stim. Pain stim.	Sleep spindles no K-complex No changes " "	" " " "
Des. 18	Pain stim. Photic stim.	" " " "	Some 4/sec. activity in the left temporal region. 8/sec. alpha activity.
1954			
Jan. 2			4/sec. activity in left temporal region with 8/sec. alpha activity.
Jan. 23			Normal 8/sec. alpha activity.
April 28	Pain stim. Acoustic stim. Smell peppermint	" " " " " "	4/sec. in left temporal region and 6/sec. generalized.
June 17	Pain stim. Photic stim. Acoustic stim.	" " No driving No changes	4/sec. in left temporal region and 6/sec. generalized.

The dates of the recordings, the results and the various activation methods employed are seen in table I.

DISCUSSION

It will appear from table I and figure 5 that no definite pathological cerebral electric activity was recorded in the patient before his loss of consciousness. The alpha activity frequency was 8 per sec. and the voltage 30 μV.

Also after the loss of consciousness a relatively regular curve was obtained, the alpha activity and voltage remaining unchanged (fig. 5).

There was a difference, however, in so far as no reaction could be elicited clinically or electroencephalographically after the application of pain and touch stimuli or smell stimuli (camphor). Light stimuli influenced the cerebral electric activity. On flicker stimulation the usual driving did not appear, but large variations in the frequency of the stimuli sometimes produced slower waves in the EEG (fig. 6).

In order to disclose possible EEG changes during sleep nearly continuous recordings were made day and night. For a few hours an ordinary sleep pattern including sleep spindles was seen (fig. 7). The sleep EEG also failed to show changes after strong pain and sound stimuli.

One of the authors (Hauge 1954) has described loss of consciousness as a complication during or after vertebral angiography. In Hauge's previous cases, however, the unconsciousness was always attended by pronounced EEG changes and by contrast filling of the posterior cerebral arteries in the angiogram. The absence in the present case of disturbance of the cerebral electric activity can be explained only by the fact that the brain area supplied by the posterior cerebral arteries had not been flushed by the contrast medium.

In the present case the autopsy findings proved the posterior cerebral arteries to be filled via the carotid system and thus explaining the non filling of these in the vertebral arteriogram. It would seem reasonable therefore to assume that the slow waves often described in states of unconsciousness are derived from structures supplied by the posterior cerebral arteries. These structures are not necessarily affected in all cases of unconsciousness, as is shown in the present case.

Similar cases of normal EEG recordings in unconsciousness patients have already been published

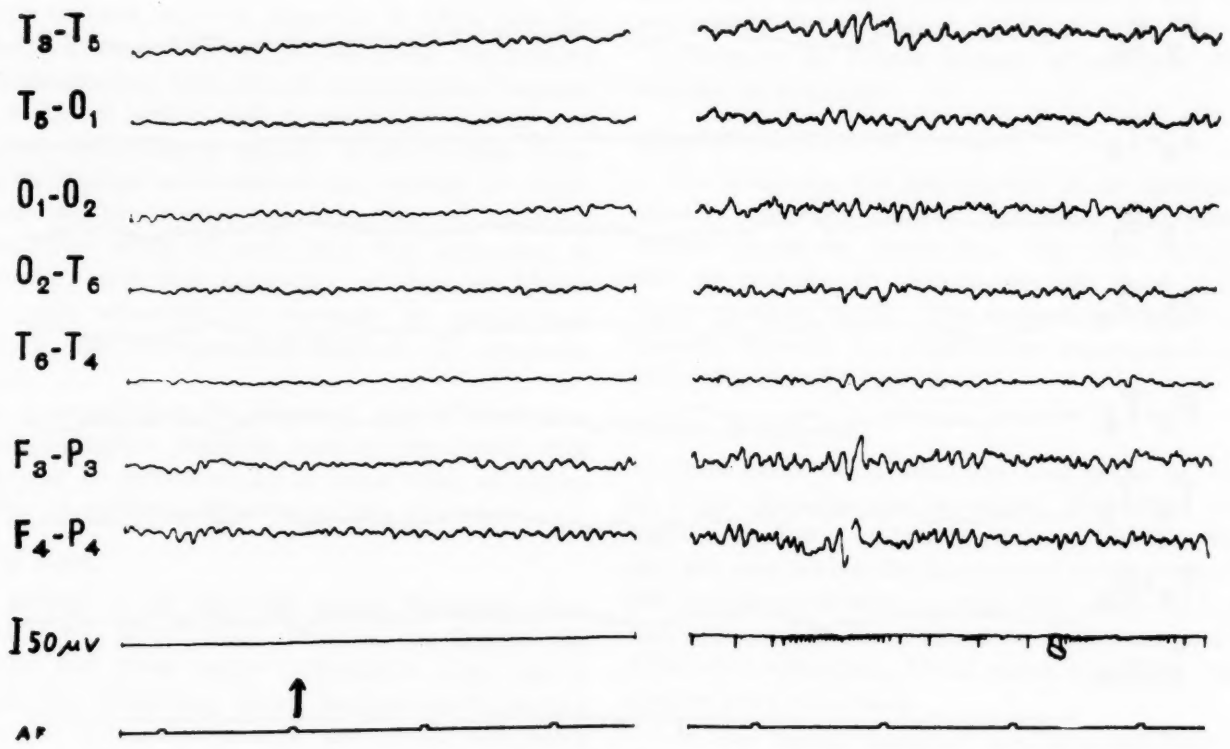


Fig. 6

Left. EEG registered 5 days after the patient became unconscious.
The arrow marks a hand-clap.
Right. EEG registered with photic stimulation the same day.

by C. Loeb and G. Poggio (1953) in a case of a ponto-mesencephalic hemorrhage, and by H: Gastaut (1954) in a case of an infiltrating glioma of the lower pons and medulla.

Considerable evidence has thus been adduced in support of the contention that unconsciousness not necessarily is attended by EEG changes when the lesion in question is situated below that area of the brain stem which depends for its blood supply on the posterior cerebral arteries.

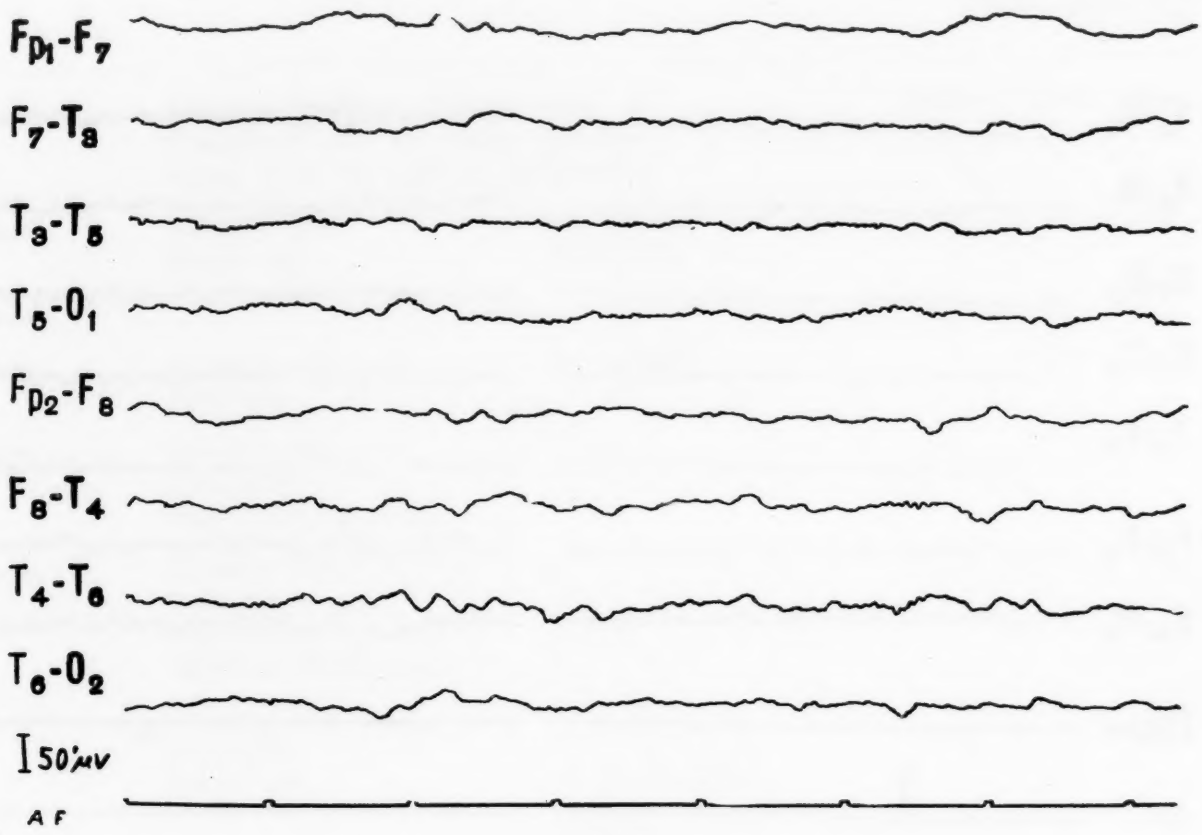


Fig. 7

EEG registered 11 days after the patient became unconscious during "sleep" with sleep spindles.

REFERENCES

BERGER, H. Uber das Elektrenkephalogram des Menschen, 4. *Mitteilung Arch. Psychiat.*, **1932**, *97*: 6-26.

GASTAUT, H. The brain stem and cerebral electrogenesis in relation to consciousness. Pp. 249-279 in *Brain Mechanism and Consciousness*, by E. Adrian, F. Bremer and H. Jasper. Blackwell scientific publications. Oxford, England, **1954**.

HAUGE, T. Catheter vertebral angiography. A clinical, angiographic and electroencephalographic study of symptoms and signs (ophthalmic migraine, visual hallucinations and agnosias, disturbances of consciousness) accompanying vertebral angiography with various contrast media, and an evaluation of its indications and diagnostic value in intracranial morbid processes. *Acta Radiologica*, **1954**, suppl. *109*: 1-219.

KAADA, B. Det anatomiske substrat for bevisstheten belyst ved nyere nevrofysiologiske studier. *Nord. Med.*, **1952**, *47*: 845-857.

LOEB, C. and POGGIO, G. Electroencephalograms in a case with ponto-mesencephalic haemorrhage. *EEG Clin. Neurophysiol.*, **1953**, *5*: 295-296.

STRAUSS, H., OSTOW, M. and GREENSTEIN, L. *Diagnostic Electroencephalography*. Grune & Stratton, New York, **1952**, 282 pp.

Reference: LUNDERVOLD, A., AUGE, T. and LÖKEN, A. C. Unusual EEG in unconscious patient with brain stem atrophy. *EEG Clin. Neurophysiol.*, **1956**, *8*: 665-670.

EFFECTS OF CHLORPROMAZINE ON THE ELECTROENCEPHALOGRAM WITH REPORT OF A CASE OF CHLORPROMAZINE INTOXICATION

JENNIE MAUCERI, M.D. and HANS STRAUSS, M.D.
Neurologic Service, Mt. Sinai Hospital, New York, N.Y.

(Received for publication : April 26, 1956)

Since the introduction of chlorpromazine, first in Europe in 1951, then in America in 1953, into the therapeutic armamentarium, it has been the subject of much laboratory and clinical investigation regarding its mode of action and diversity of clinical uses (Koetschet 1955; Moyer 1955). While several European investigators have studied the effects of chlorpromazine on the electroencephalogram of epileptic subjects, little work of such kind has appeared in this country, with the exception of that of Merlis (1955), who observed an increase in paroxysmal patterns in the electroencephalogram of psychotic epileptics.

The observation to be reported reveals that electroencephalographic patterns usually associated with epilepsy can be produced by a toxic dose of chlorpromazine in subjects free from this disorder.

Report of Case.

The patient, a 19 year old college freshman, was admitted to the Mount Sinai Hospital on October 12, 1955. She had been under psychiatric care for a psychoneurotic condition which became overt during an otherwise normal pregnancy and which continued after delivery. She had been taking chlorpromazine, 25 mgm q.i.d., since May 1955, and although she sometimes skipped the drug for a week at a time, she had been taking it regularly for the month preceding her admission into the hospital.

Present illness.

At 2 p.m. of October 12, 1955, she took several handfuls of chlorpromazine pills in a suicidal attempt. At first she felt elated and went window shopping, but by 4:30 p.m. she became sleepy, ''groggy'' (not dizzy), and her heart was pounding. She went to her physician's home and was made to vomit with hot water. Her remembrance of this at a later date was vague. At 9 p.m. she was admitted to the hospital.

Past history.

The patient is the third of three children. She had pertussis at age 8; German measles at 9; measles and mumps at 14, followed two weeks later by infectious hepatitis; and infectious mononucleosis at age 17. None of these were associated with alteration of consciousness, and there were no sequaelae. There was no history of head injury at birth or subsequently, fainting attacks, migraine, or any type of paroxysmal disorder.

There is no family history of epilepsy, fainting attacks, or migraine.

Physical examination.

On admission the patient was in no distress, lying quietly, apparently asleep, but could be aroused and answer questions rationally. The oral temperature was 99 degrees F., respiration 22, pulse 100, and blood pressure 92/68. The systemic examination was normal, however the pupils were constricted and the reflexes generally depressed.

Course in hospital.

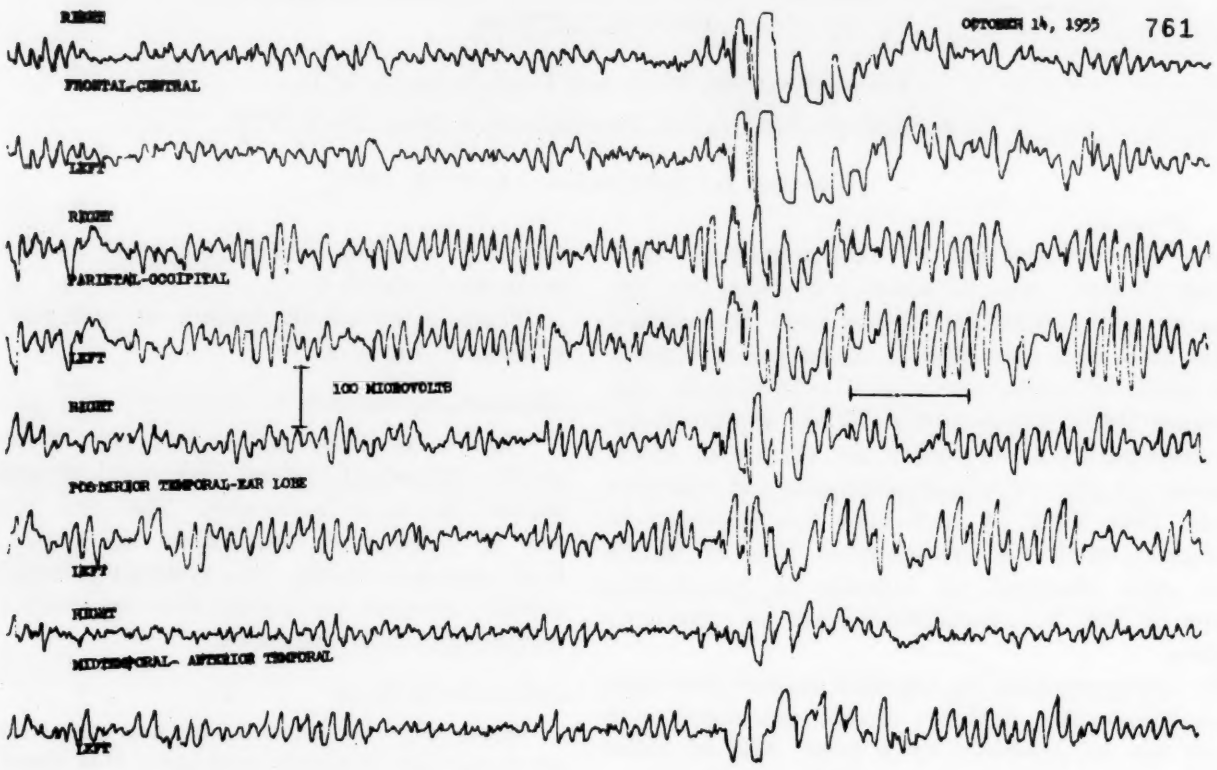
Soon after her arrival she was given an infusion of 5 per cent dextrose in water. Her blood pressure stabilized readily at 100/70, pulse at 90. By the next day she was taking fluids p.o. and voiding adequately. She continued to sleep soundly but awoke at intervals and appeared to be oriented to self, time and place. Admission urinalysis, blood count and liver function studies were all normal.

On her second hospital day, she was able to sit up, and her only complaint was numbness of the tongue. Dysarthria, and a papular nonpuritic rash on the left volar forearm were observed. A neurologic examination showed no evidence of neurologic deficit, especially in regard to basal ganglia or bulbar signs. While in the electroencephalographic laboratory she appeared to be somewhat dazed, and her memory of this event as well as others was hazy when she was questioned regarding them one week later.

She was discharged on October 15.

The first electroencephalogram obtained October 14, 1955 revealed a moderate number of diffuse and symmetrical bursts of spike and wave patterns with frequencies of 3 to 4 per sec. also bursts of 3 c/sec. activity, which were predominantly symmetrical, but also shifted from one side to the other without any permanent focal accentuation (fig. 1, 2).

The second electroencephalogram was taken 12 days later, on October 26, 1955, Serpasil 0.25 mg. t.i.d. having been substituted for the chlorpromazine. This record did not show any spike and wave activity or any other abnormality, but occasional sleep patterns (fig. 3, 4).



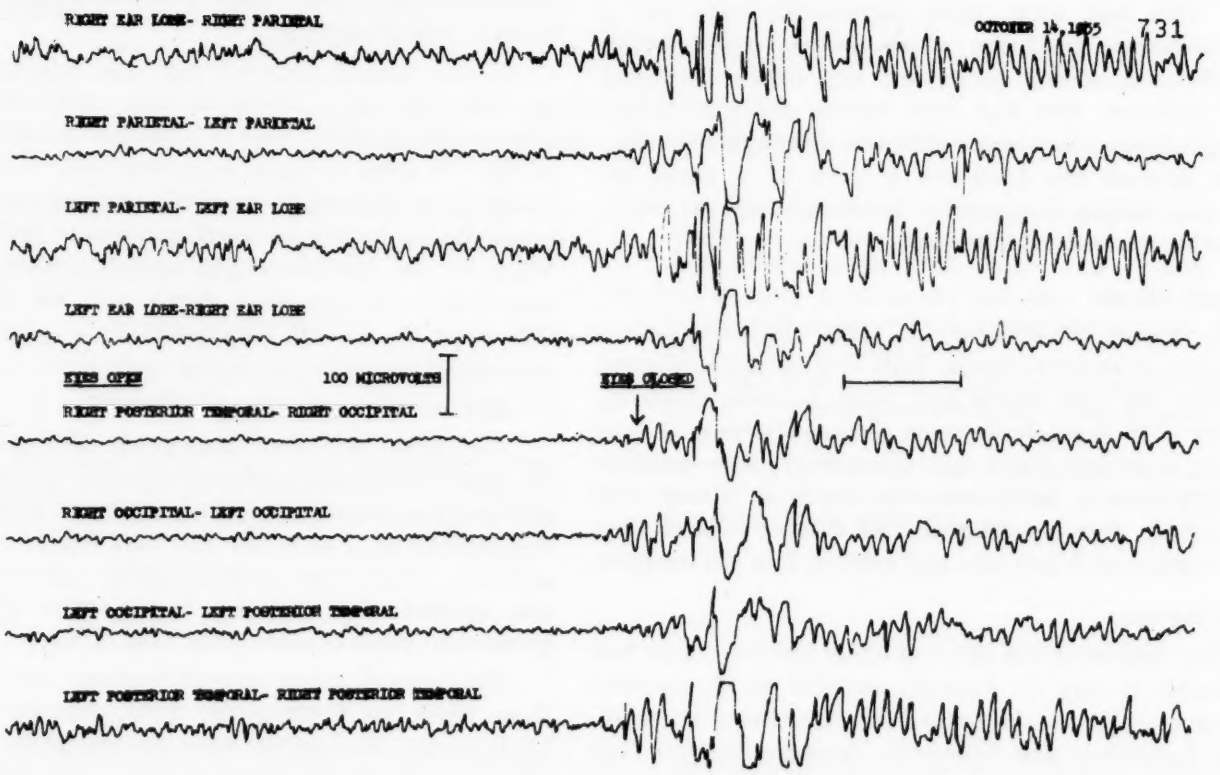

RIGHT EAR LOBE- RIGHT PARIETAL
RIGHT PARIETAL- LEFT PARIETAL
LEFT PARIETAL- LEFT EAR LOBE
LEFT EAR LOBE-RIGHT EAR LOBE
EYES OPEN
100 MICROVOLTS
EYES CLOSED
RIGHT POSTERIOR TEMPORAL- RIGHT OCCIPITAL
RIGHT OCCIPITAL- LEFT OCCIPITAL
LEFT OCCIPITAL- LEFT POSTERIOR TEMPORAL
LEFT POSTERIOR TEMPORAL- RIGHT POSTERIOR TEMPORAL

Fig. 1 and 2

Electroencephalograms under the influence of chlorpromazine.

DISCUSSION

This neurotic girl attempted suicide with an unknown quantity of chlorpromazine. At first she experienced transient elation which terminated in a state of impaired consciousness. She showed fragmentary memory for some time following the intoxication as evidenced by an amnesia for events occurring during the period of her hospitalization, including the time when the first electroencephalogram was obtained. This electroencephalogram showed diffuse spike and wave patterns which were not present in the second electroencephalogram taken 12 days later. This indicates that chlorpromazine in large doses can evidently produce, in a patient without epilepsy or organic brain disease, a type of electroencephalographic abnormality usually found in epileptics.

Chlorpromazine used in the treatment of disturbed psychiatric patients has proven its quieting effect, especially in states of psychomotor excitement and mania (Leumann *et al.* 1954; Goldman 1955; Barsa *et al.* 1955). Electroencephalographic studies by various investigators reflect this tranquillizing effect. In a study by Liberson (1955) chlorpromazine administered to 19 chronic schizophrenic patients (up to 400 mg. q.d.) for 5 months, produced slight changes in the electroencephalogram and these were related to the alpha activity, producing a regularizing effect on the alpha rhythm, reflecting the clinical tranquillization of the patients.

Lehmann and Hanrahan (1954) report that electroencephalographic studies in chlorpromazine treated patients, tend to show "clear tracings comparatively free from muscle artifacts and tension discharges" without alteration of "the basic character of the individual electroencephalogram as long as the subject is awake". According to Terzian (1952) chlorpromazine produces an electroencephalographic pattern similar to normal sleep. Monroe *et al.* (1955) in cortical and subcortical studies on 4 monkies and 4 humans, found that 50-100 mg. of chlorpromazine given intravenously produced "a relaxed record with short bursts of drowsiness and occasional light sleep, during which time the subject was motionless, with eyes closed, appearing asleep, but easily aroused".

Therefore all these electroencephalographic studies in patients and animals presumably without epilepsy or organic brain disease demonstrate such changes in the electroencephalogram which are usually associated with relaxation and sleepiness and do not describe any abnormalities induced by chlorpromazine.

On the other hand, in epileptics, Merlis (1955) observed that chlorpromazine, while relieving anxiety and agitation, could also accentuate the typical electroencephalographic patterns of epileptic activity, and produce convulsions in 2 per cent of his 150 epileptic patients. Bente (1954) also reports an increase in electroencephalographic abnormality with chlorpromazine. This is in agreement with the clinical observation of Broussolle (1955) who found that chlorpromazine aggravates epileptic disturbances and increases the frequency of episodes. Similarly, Bonafede (1955) notes that chlorpromazine does not appreciably reduce the frequency of seizures in psychotic epileptics when maintenance therapy of phenobarbital or Dilantin is reduced. Lomas *et al.* (1955) in a study of the complications of chlorpromazine therapy in 800 mental hospital patients, report the occurrence of epileptic fits in 10 of these patients. "In only one of these ten patients... had no tendency to epilepsy been observed, but in all of them fits were very rare, had been absent for a long time, and with one exception, have not recurred since treatment with chlorpromazine was stopped." "The fact that the epileptic fits had no relationship either to dosage or to duration of treatment suggests that chlorpromazine has epileptogenic properties which may lead to manifest fits in susceptible people." No electroencephalographic report is made in these cases.

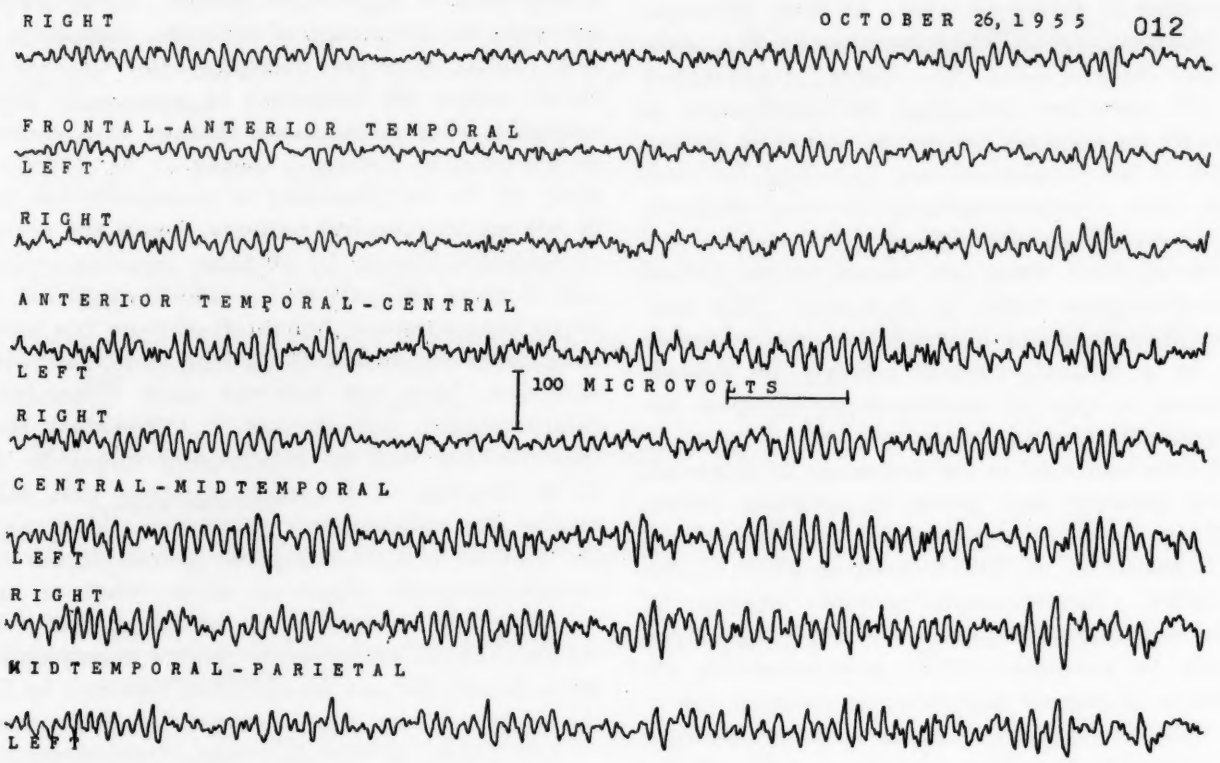
While there seems to be no doubt that chlorpromazine induces or increases fits in known epileptics, there is only the one nonepileptic, reported by Lomas, in whom seizures were induced by chlorpromazine.

Until now, no case has been reported where electroencephalographic abnormalities indicative of epilepsy were produced by chlorpromazine in a nonepileptic. We believe our case is the first to be reported.

The provocation of focal electroencephalographic abnormalities in patients with focal cortical seizures has been demonstrated by several European authors. Mayr and Leihner (1954), made a comparison of chlorpromazine, Metrazol, and Pentothal, in regard to their ability to activate the electroencephalogram in patients with temporal lobe epilepsy. Focal epileptic patterns including spikes were induced in 86 per cent of patients with chlorpromazine, in 36 per cent with Metrazol, and in 32 per cent with Pentothal. In 8 patients in whom chlorpromazine induced temporal spikes, these were not associated with a sleep pattern. A corresponding observation was made by Bente (1954) in one of his cases.

SUMMARY

All these observations including our own show that the clinical and electroencephalographic effects of chlorpromazine are extremely complex. Chlorpromazine has: (1) an effect similar to that seen in many sedative drugs; (2) effects similar to that of Metrazol which has been shown to provoke localized spikes in patients with focal seizures (Kaufman *et al.* 1947) and diffuse spike and wave patterns in nonepileptic subjects (Strauss *et al.* 1952). The fact that the provocation of focal spikes by chlorpromazine is not associated with clinical or electroencephalographic signs of sleep makes its activating effect



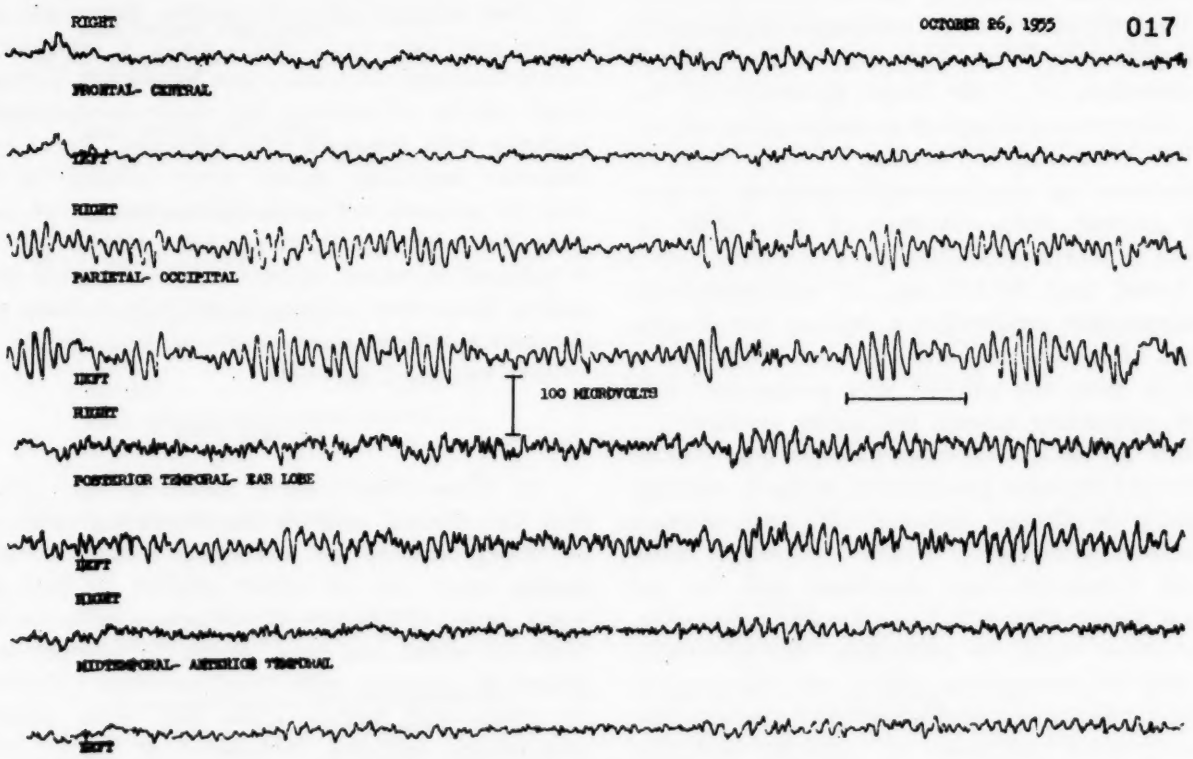


Fig. 3 and 4

Electroencephalograms after withdrawal of chlorpromazine.

very similar to that of Metrazol. According to the literature, it seems to be even more promising in the provocation of focal spikes.

We cannot make any statement as to the amount of chlorpromazine necessary to produce diffuse spike and wave patterns either in normals or epileptics, but can state that such patterns can be produced in normals. The question of the quantity is open for further investigation. So also is the question of the point of attack of chlorpromazine on the central nervous system, on which several assumptions have been made, none of which, however, explains all the observed facts.

REFERENCES

BARSA, J. A. and KLINE, N. S. Combined reserpine-chlorpromazine in treatment of disturbed psychotics. *Arch. Neurol. Psychiat.*, Chicago, **1955**, *74*: 280-286.

BENTE, D. Zur Wirkung des Phenothiazinkörpers Megaphen auf das menschliche Hirnstrombild. *Arzneimittel-Forschung*, **1954**, *4*: 418-423.

BONAFEDE, V. I. Chlorpromazine (thorazine) treatment of disturbed epileptic patients; preliminary report. *Arch. Neurol. Psychiat.*, Chicago, **1955**, *74*: 158-162.

BROUSSOLLE, B. Chlorpromazine in Psychiatry. *Intern. Rec. Med. Gen. Pract. Clin.*, **1955**, *168*: 327-338.

GOLDMAN, D. Treatment of psychotic states with chlorpromazine. *J. A.M.A.*, **1955**, *157*: 1274-1278.

KAUFMAN, I. C., MARSHALL, C. and WALKER, A. E. Activated electroencephalography. *Arch. Neurol. Psychiat.*, Chicago, **1947**, *58*: 533-549.

KOETSCHET, P. Can it be said that chlorpromazine has specific properties ? *Intern. Rec. Med. Gen. Prac. Clin.*, **1955**, *168*: 295-300.

LEHMANN, H. E. and HANRAHAN, G. E. Chlorpromazine; new inhibiting agent for psychomotor excitement and manic states. *Arch. Neurol. Psychiat.*, Chicago, **1954**, *71*: 227-237.

LIBERSON, W. T. Effects of chlorpromazine on the electroencephalogram and skin galvanic activity. *EEG Clin. Neurophysiol.*, **1955**, *7*: 474.

LOMAS, J., BOARDMAN, R. H. and MARKOWE, M. Complications of chlorpromazine therapy in 800 mental hospital patients. *Lancet*, **1955**, *268*: 1144-1146.

MAYR, F. und LEIHNER, H. Zur Frage der Provokation der Temporallappen-Epilepsie im Elektroencephalogramm. *Wiener klin. Woch.*, **1954**, *66*: 903-906.

MERLIS, S. *Chlorpromazine and Mental Health*, Lea and Febiger, **1955** (p. 60).

MONROE, R. R., HEATH, R. G., MICKLER, W. A. and MILLER, W. A comparison of cortical and subcortical brain waves in normal, barbiturate, reserpine and chlorpromazine sleep. *Ann. N.Y. Acad. Scien.*, **1955**, *61*: 56-71.

MOYER, J. H. The pharmacology of chlorpromazine. *Intern. Rec. Med. Gen. Prac. Clin.*, **1955**, *168*: 301-311.

STRAUSS, H., OSTOW, M. and GREENSTEIN, L. Diag*nostic Electroencephalography*. Grune and Stratton, **1952** (p. 48).

TERZIAN, H. Electroencephalographic investigation of the central action of Largactil. *Rass. neurol. vegetat.*, **1952**, *4*: 211-215.

Reference : MAUCERI, J. and STRAUSS, H. Effects of chlorpromazine on the electroencephalogram with report of a case of chlorpromazine intoxication. *EEG Clin. Neurophysiol.*, **1956**, *8*: 671-675.

PONTINE OR "RETICULAR" EPILEPSY : REPORT OF A CASE

CH. ARAKI, M.D., K. SAKATA, M.D. and T. KUROKI, M.D.
First Surgical Division, Kyoto University Medical School, Kyoto, Japan

(Received for publication : April 18, 1956)

This report concerns a patient of probable pontine epilepsy of traumatic origin.

Patient E. K., a laborer 28 years old, was admitted to our clinic on April 23, 1955, with chief complaint of convulsive attacks of the right half of the body with loss of consciousness. In August 1954, he was struck on his chest by a falling wood weighing about 70 kg. and lost consciousness for several minutes. He noticed after trauma reduced sensibility of right upper and lower extremities and of left half of face, and sometimes also pins and needles in the latter region. Since December 1954, he has had epileptic seizures at intervals of about a week.

Previous and family histories show nothing particular. On admission, the patient's seizure was seen to occur in the following pattern.

He suddenly loses consciousness and falls down. After 2-15 sec. the head is turned to the left and right upper and lower extremities are tonically extended. Right extremities are then lightly bent at the elbow and knee, showing intermittent twitchings. Left extremities are flaccid throughout. This fit can be precipitated by pain delivered to various parts of the body, if the pain is of sufficient intensity and it seems that the stronger the stimulus, the longer the duration of seizure.

In a minor seizure of short duration (10-20 sec.) there is mere unconsciousness [1] with general flaccidity, whereas in a longer one (of about 3 min. duration) tonic spasms of the right half of the body alternate with general flaccidity. The same seizure can be precipitated by compression of carotid artery, especially on the left side, but no marked change is noticed in pulse rate or blood pressure. No terminal sleep takes place.

There are no scars or deformities of head. Tactile,

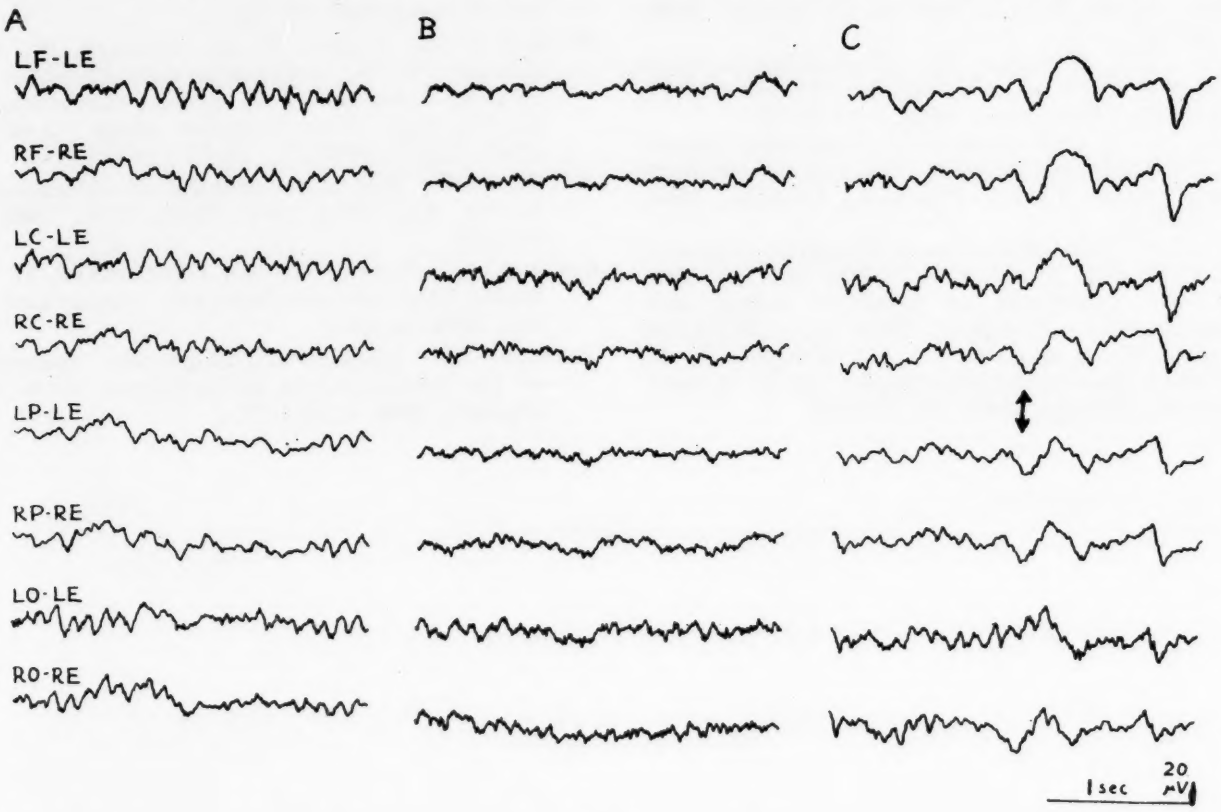


Fig. 1
A : Before subcutaneous injection of 0.5 cc. of 50 per cent alcohol.
B : 30 sec. after injection. The patient is unconscious. No motor phenomena.
C : 1 min. 30 sec. after injection. At arrow the patient is awakened and responding to calling by his name. (Slow positive deflections are blinking artifacts.) Abbreviations : F, frontal. C, central. P, parietal. O, occipital. E, ear lobe.

1 Unresponsive to nociceptive stimuli, for example to pin prick. No response to calling by name and no memory. Corneal reflex, diameter of pupils and their reaction to light are normal. Eyeballs are lightly deviated to left and downward, but nystagmus is not present.

pain and thermal sensibilities are reduced in the left half of the face and in the right half of the neck and trunk and in the right upper and lower extremities. Motility of extremities suffers no remarkable impairment. Pressure of cerebrospinal fluid is 170 mm. of water. The left carotid angiogram as well as the pneumo-ventriculogram are normal.

Interseizure EEG shows diffuse 4-10/sec. (mainly 6-7/sec. with some alpha) waves below 50 μV. and no distinct seizure activity can be recorded (cf. fig. 1A). Upon delivering painful stimuli — for example, pressure on the suture line of the trephine wound for ventriculography, subcutaneous injection of 50 per cent alcohol — or compression of carotid artery, the EEG shows immediately more or less marked desynchronization, corresponding to the beginning clinical seizure (fig. 1B). No distinct spike discharges can be seen in ictal as well as pre- and postictal periods.

In injecting Pentothal slowly, a relatively small dose (60 mg.) can induce unresponsiveness accompanied by low voltage fast EEG with suppression of preexisting slow components — at a stage before appearance of marked barbiturate fast waves. In the stage of anesthesia showing prominent slow waves, heavy nociceptive stimuli cannot elicit any marked changes both in EEG and in clinical features, whereas in the succeeding regressive stage with predominant barbiturate fast waves (the patient is still unconscious) painful stimuli induce a seizure.

After blocking stellate ganglia on both sides by Xylocaine (May 24) he felt fine in his head and the attack was hardly precipitated. Accordingly, left stellate ganglionectomy was carried out on May 27. Prominent left Horner's sign appeared after operation, and we became unable to precipitate the seizure by any nociceptive stimuli. In postoperative EEG alpha waves became more apparent. Since leaving the hospital (June 14) he has been feeling agreeable up to the present time (9 months later). He has had two mild fits, when fatigued with excessive labor. Crossed hemihypesthesia is persisting.

DISCUSSION

Penfield and Erickson (1941) reported several cases of mesencephalic seizure. Although the seizure of the present patient is different from Penfield's typical decerebrate attack in some aspects — for example, the lack of pronation of arm and of plantar flexion of foot and the presence of twitching — there seems to be no doubt about the location of the lesion in the left pontine region in view of the presence of crossed hemihypesthesia. Restriction of the tonic attack to the right half of the body and turning of the head to left (Bazett and Penfield 1922) may also favor this assumption, and paresthesia of the left half of the face suggests irritative nature of the lesion. Because of the normal pneumoventriculogram, the normal angiogram and the absence of any distinct spike or focalized dysrhythmia, there seems to be no reason for assuming any cortical lesion.

Of special interest in this case is the precipitation of seizure — especially of loss of consciousness — by pain. The desynchronizing tendency of EEG by pain in this case may be the alerting reaction effected by impulses passing through the route of sensory collaterals (Moruzzi and Magoun 1949; French, Verzeano and Magoun 1953). Important, however, is the fact that this EEG change is accompanied by loss of consciousness instead of alerting.

As the activation of EEG can be elicited by wide varieties of stimuli delivered to the reticular system, it is possible that in case of epileptic bursts of the arousal system the EEG is desynchronized while consciousness is impaired as a result of disturbance of the normal function of that system. Thus a type of epilepsy such as in this case may be named "reticular epilepsy".[1] As to the reason for the excellent recovery by stellate ganglionectomy, nothing definite can be said at present.

SUMMARY

A case of probable traumatic pontine epilepsy has been presented. In this case seizure was easily precipitated by pain, and desynchronization of EEG was seen during seizure. The disease was improved by cervical sympathectomy. It is supposed that desynchronization of the EEG accompanying an unconscious fit may be characteristic of epileptic bursts in the reticular system i.e. "reticular epilepsy".

REFERENCES

BAZETT, C. and PENFIELD, W. A study of the Sherrington decerebrate animal in the chronic as well as the acute condition. *Brain*, **1922**, *45*: 185-264.

FRENCH, J. D., VERZEANO, M. and MAGOUN, H. W. An extralemniscal sensory system in the brain. *Arch. Neurol. Psychiat.*, Chicago, **1953**, *69*: 505-518.

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

PENFIELD, W. and ERICKSON, T. C. *Epilepsy and Cerebral localization*, Charles C. Thomas, Springfield, Ill. **1941**.

1 In cases showing such symptoms as in the present patient hysteria should be taken into consideration, but this will be excluded in our case because seizure could be precipitated — or rather facilitated — at the stage of light barbiturate anesthesia when he was unconscious.

Reference: ARAKI, CH., SAKATA, K. and KUROKI, T. Pontine or "reticular" epilepsy: report of a case. *EEG Clin. Neurophysiol.*, **1956**, *8*: 676-677.

EEG CHANGES IN AMYOTROPHIC LATERAL SCLEROSIS

WALTER J. FRIEDLANDER, M.D.
Neurology Section, VA Hospital, San Francisco, Calif.

(Received for publication : April 9, 1956)

It is difficult to find a disease that directly or indirectly involves the central nervous system in which the associated EEG findings have not been the subject of at least one report. It was therefore surprising, when in answer to a specific case, search of the literature on EEG and on amyotrophic lateral sclerosis failed to reveal any such information except for one paper and one case report (Valentiejus 1956) in which a normal EEG was commented upon in passing. Guillain, Bertrand and Godet-Guillain in 1940 described EEG abnormalities in 3 out of their 6 cases; the types of abnormalities were: anterior slowing, paroxysmal activity, and 2-3 per sec. fronto-parietal spike-wave complexes.

There is, of course, reason to suspect that some alteration of the EEG might occur in this disease since brain changes are found even though there is a difference of opinion as to how much and how often the cerebral cortex *per se* is usually involved. From experience with other central nervous system degenerative diseases, it is expected that if there are EEG changes in this disease they are probably not very great ones.

RESULTS

The EEGs of 18 consecutive patients who had amyotrophic lateral sclerosis or progressive spinal muscular atrophy were reviewed. The history and the locations of the motor neuron involvement in each case is summarized in table I.

The EEGs of 12 patients were normal; the findings in the remaining 6 are as follows:

(1) J. A. M. — A 55 year old male who in addition to his neurological disease had, on admission, a blood pressure of 160/94 as well as an abnormal EKG which was interpreted as being consistent with an old myocardial infarction. He eventually had definite evidence of upper motor neuron, bulbar lower motor neuron and spinal lower motor neuron involvement. His EEG on 11-8-48 was normal; at that time he presented only upper motor neuron signs. On 11-2-49 his EEG was interpreted as being mildly abnormal because of some scattered theta and poorly defined anterior paroxysmal activity. In the interim between the first second EEG, bulbar and spinal lower motor neuron disease had become evident and there was also some change in his personality characterized by unwarranted laughter and unusual irritability. Three subsequent recordings obtained over the next 9 months did not show any significant change; clinically his disease progressed steadily during this time and he became more irritable and tearful. Post-mortem obtained 8 months after his last EEG showed loss of cortical neurons as well as bulbar and spinal lower motor neuron changes.

(2) R. E. H. — A 46 year old male who had definite neurological signs of upper motor neuron and spinal lower motor neuron disease and questionable bulbar lower motor neuron involvement. He was admitted on 12-4-52, had an EEG 4 days later, and died 3 days after that. On admission he suffered from sufficient respiratory difficulty to warrant his being placed on the seriously ill list. His EEG showed some scattered theta activity and the record was classified as mildly and diffusely abnormal. He died of respiratory failure.

(3) M. E. D. — A 57 year old male with signs of spinal lower motor neuron disease only. In July 1954, he suffered from severe enough respiratory distress to necessitate his being placed in a respirator; he was confused and hallucinating on 8-12-54 and it was felt that this mental state was due to cerebral anoxia. His first EEG was obtained on 6-15-54 and was normal; the second record was obtained on 9-3-54 at which time a 6 per sec. rhythm with scattered 4-5/sec. activity was seen.

In addition to these three patients with frankly, though mildly abnormal EEGs, three other patients had minor changes in their EEGs sufficient to classify them as borderline, e.g. very poorly defined paroxysmal activity and/or minimal increase in theta activity. These changes might have been considered insignificant by some electroencephalographers. As for the clinical correlations of these borderline EEGs, one patient had not very far advanced spinal lower motor disease and the other two had evidence of both upper motor neuron and spinal lower motor disease; in no case was there evidence of significant respiratory difficulty.

DISCUSSION

Because of the nature of EEGs, the definition of what is abnormal is in no way settled. A review of all the EEGs of these 18 patients by another electroencephalographer may have yielded a different set of impressions. Therefore, it would be unwise to interpret the results of this survey in any statistical terms. However, it is evident that definite electroencephalographic changes are at least unusual in amyotrophic lateral sclerosis except when there is

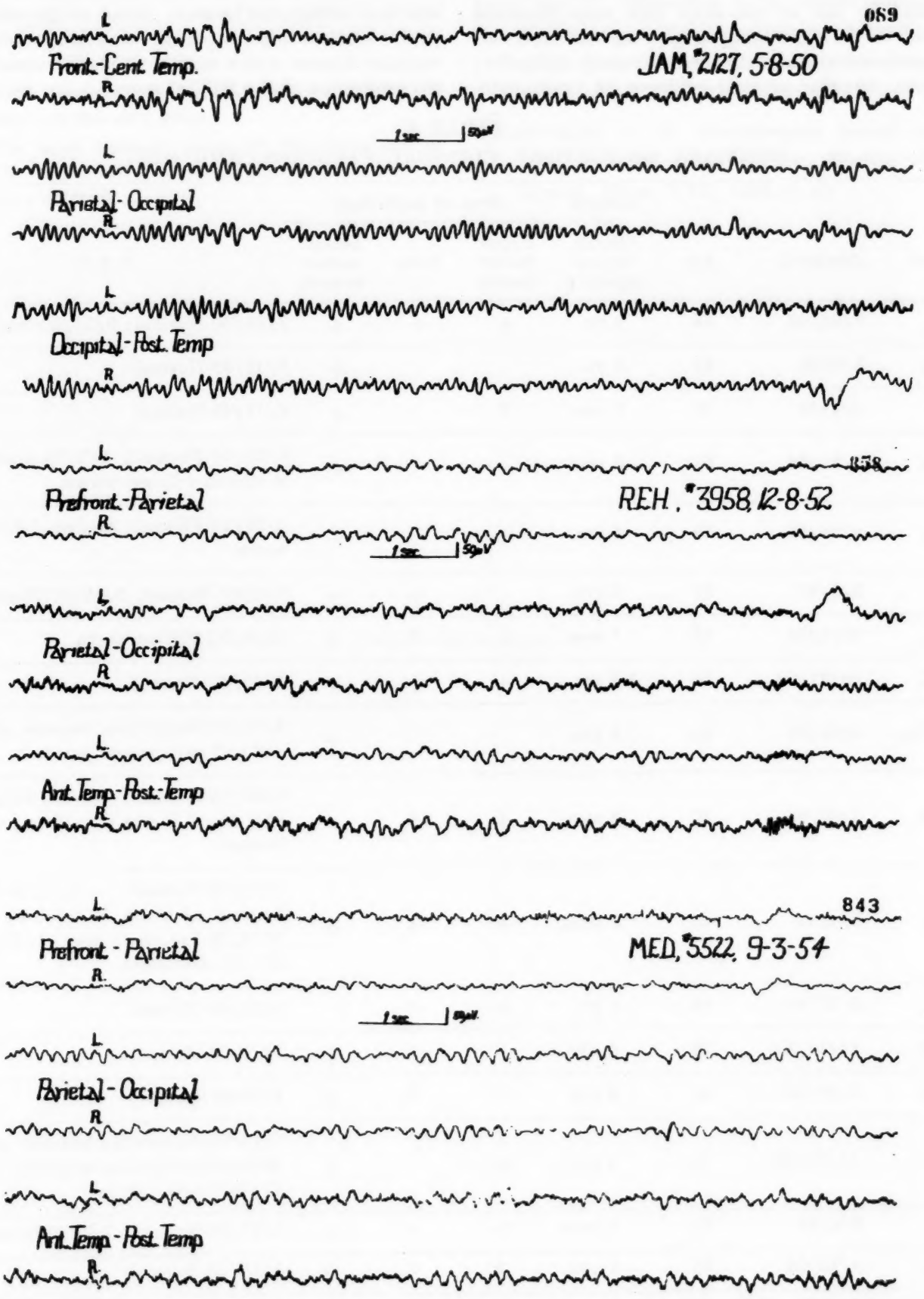


Fig. 1

Sample EEG tracing from the 3 patients who had abnormal records.

probable cerebral anoxia due to respiratory difficulty secondary to the basic pathological process. This was illustrated by two of the cases that were discussed in detail. In the other case, the slowing was apparently unassociated with significant respiratory difficulty; there was, however, clinical evidence of brain pathology other than motor neuron disease which was manifest by an alteration of personality so that it was not unlike that seen in cases of pseudo-bulbar palsy. Also, in this case, there was evidence of cardiovascular disease which may have played some role in the production of the EEG changes.

TABLE I

SUMMARY OF HISTORY, CLINICAL FINDINGS, AND EEGs

Patient	*Admitt'd*	*Age*	*Length of illness before admis'n*	*Area of pathology*			*E E G*
				Upper motor neuron	*Bulb*	*Lower motor neuron*	
E.C.A.	7/25/55	58	1 yr.	+	+	+	7/28/50-Normal; 9/21/50-Normal
A.M.B.	8/9/49	57	1 yr.			+	8/12/49-Normal
O.L.B.	4/4/49	37	6 yrs.	?		+	4/11/49-Normal
M.E.D.	6/11/54	57	3 yrs.			+	6/15/54-Normal; 9/3/54-6/sec. with scattered 4-5/sec. waves
A.H.G.	6/26/51	59	5 yrs.	+		+	6/27/51-Minimal random 5-6/sec. waves
M.G.	8/5/47	57	5 yrs.		+	+	8/4/47-Normal; 8/20/47-Normal
R.E.H.	12/4/52	46	7 mos.	+	?	+	12/8/52-Diffuse theta
K.H.K.	10/31/52	56	1.5 yrs.	+	+	+	11/5/52-Normal
J.E.McA.	8/19/53	26	8 yrs.			+	8/21/53-Borderline because of poorly defined paroxysmal bursts
M.T.M.	4/20/55	22	8 mos.	+	?	+	4/28/55-Normal; 6/13/55-Questionably slight increase in theta; 6/20/55-Normal
J.A.M.	3/4/49	55	7 mos.	+	+	+	11/8/48-Normal; 11/2/49-Abnorm. because of theta; 2/6/50-As before; 5/18/50-Inc. theta over 11/49; 8/7/50-As before
R.M.	9/27/49	58	1 yr.	+	?		9/22/49-Normal
J.M.M.	10/14/54	38	2 wks.	+	+	+	11/3/54-Normal
T.E.N.	7/30/49	27	5 yrs.		?	+	8/8/49-Normal
P.L.T.	10/24/55	34	2 yrs.	+		+	5/18/53-Borderline because of poorly defined paroxysmal activity; 11/10/55-As before
C.P.	6/1/56	55	6 mos.	+	+	+	6/27/56-Normal; 7/6/56-Normal
F.H.S.	4/12/56	54	4 yrs.	?	0	+	4/18/56-Normal
J.B.T.	5/1/56	50	7 mos.	0	+	+	5/5/56-Normal; 6/1/56-Normal

+ - Area definitely involved, ? - Area questionably involved.

SUMMARY

1. The EEGs in 15 cases of amyotrophic lateral sclerosis or progressive spinal muscular atrophy have been reviewed.

2. EEG changes are unusual and when they do occur, they are not very great.

3. The most common cause of the alteration of the EEG is probably cerebral anoxia secondary to respiratory difficulty.

REFERENCES

GUILLAIN, G., BERTRAND, I. et GODET-GUILLAIN, J. Modifications de l'électroencéphalogramme au cours de la sclérose latérale amyotrophique. *C. R. Soc. Biol.*, Paris, **1940**, *134*: 462.

VALENTIEJUS, J. A. Amyotrophic lateral sclerosis with cortical atrophy. *Proc. Weekly Seminar Neurol.*, Hines, VAH, **1956**, *8*: 20.

Reference: FRIEDLANDER, W. J. EEG changes in amyotrophic lateral sclerosis. ***EEG Clin. Neurophysiol.***, **1956**, *8*: 678-681.

LOSS OF RIGHT HEMISPHERE DUE TO NATURAL CAUSES

Absence of Functioning Right Thalamus with Related Thalamic Syndrome and Continued Recognition of Painful Stimuli on the Hemiplegic Side

STUART WEISS, M.D., IRWIN LEVY, M.D., DAVID SMITH, M.D.[1]
and JAMES L. O'LEARY, M.D.
Division of Neurology, Washington University School of Medicine, St. Louis, Mo.

(Received for publication : March 26, 1956)

This report concerns the loss of a right hemisphere as the result of a cerebral hemorrhage. It is believed to have significant neurophysiological implications because with only a small portion of the right posterior midline thalamus remaining (the relay and association nuclei being missing in their entirety), the subject could still experience pain upon her hemiplegic side, and had a thalamic syndrome of unremitting burning pain throughout her 11-year survival period. The midline remainder of the right thalamus was so sparsely populated by cells and fibers that it seems unlikely to have participated in functioning. Thus the recognition of pain upon the affected side was likely mediated either through the homolateral thalamus, or, if contralaterally, by the brain stem mechanism. Anatomically the case approximates one reported by Piorry in *La Lancette Française* for 1829. In the words of that narrator: "It was not a brain that I found but only the half of one." There, too, the loss was a right-sided one. The intellect of the subject is said to have been unimpaired.

Case Report.

A female patient had a questionably relevant hospital admission in 1937 (age 40). At that time she complained of life-long severe, intermittent left temporal headaches of migranoid character. A usual headache lasted 1 - 4 days and was accompanied by nausea and vomiting. Her husband describes her as ordinarily having a sociable out-going personality, and she was a superior bridge player. In 1940 she was admitted to St. Luke's Hospital, St. Louis (service of Dr. Ronald Klemme) in a semi-comatose state, suspected of having a right parietal lobe tumor. Craniotomy following ventriculography revealed a massive right subdural hematoma extending from the mid-parietal region to the frontal tip. The right frontal lobe was pulpy and a gush of blood appeared from its interior. To obtain hemostasis a frontal lobectomy was done, excluding the motor cortex but removing all of the lobe anterior to it. The vascular sources of the hemorrhage were impossible to identify at the time. Systemically, post-operative recovery was uneventful; but from the beginning both her cerebration and her speech were markedly slow. She is also described as having had a childish personality post-operatively, with flight of ideas and inability to concentrate upon one subject for any length of time. She was also said to be totally unable to grasp abstract ideas or to do conceptual thinking. She became enraged on minor frustration, and wept frequently. These personality alterations remained essentially unchanged throughout the survival period. She continued to play bridge with some coaching, but there was marked reduction in her ability and in her bidding judgement.

One month post-operatively the subject commenced to experience intermittent burning pain in her left arm and leg. By then her left arm was becoming rigidly fixed in a hemiplegic posture. As time progressed the burning pain came to affect her whole left side, and changed from paroxysmal to constant character. It was relieved only by opiates. In 1944 she was readmitted to Dr. Klemme's service for a right parietal cortex ablation (Gutiérrez-Mahoney 1944) with the hope that the procedure would relieve the unremitting left-sided pain. To the surgeon's surprise the right hemisphere was absent with the exception of a small piece of temporal lobe and a golf-ball sized piece of occipital lobe. The circle of Willis was readily exposed to view and the middle cerebral artery was identified as the likely source of the hemorrhage that had occurred four years previously. It was ligated close to its source. Post-operatively, the pain was unrelieved.

The last complete neurological examination was accomplished in 1952, the year of her death from a coronary thrombosis, and is reported here principally in its sensory detail. There was anosmia on the right, and almost complete loss of vision in the right eye, and of the temporal field of the left eye. Sensory loss on the left side of the face was definite but less marked than over the left side of the body. Upon the body there was a loss of pin prick, temperature and light touch. Nevertheless she complained of a constant burning pain sensation there which was increased each time she was stimulated with a pin. This recognition that she was being stimulated was

1 Now of the University of Virginia School of Medicine, Charlottesville, Va.

well-demarcated at the midline, and on the upper extremity was invariably referred to the nearest joint. Thus, within limits, she could localize the area of stimulation, and the nearer the point stimulated was to the locale of a joint the more accurate her localizing ability appeared. Deep muscle pressure and joint movement were also described as very painful upon the left side, and poorly localized. Speech was dysarthric but intelligible.

Anatomical Findings.

At post-mortem the right hemisphere was entirely missing with the exception of small detached fragments (0.5 to 1.5 cm.) of cortex tentatively identified as lingual gyrus and gyrus rectus. The right olfactory nerve was missing and the right optic nerve was reduced to thread-like dimension. The only remainder of the right thalamus was a small nubbin attached to the mesial wall of the left one, and this

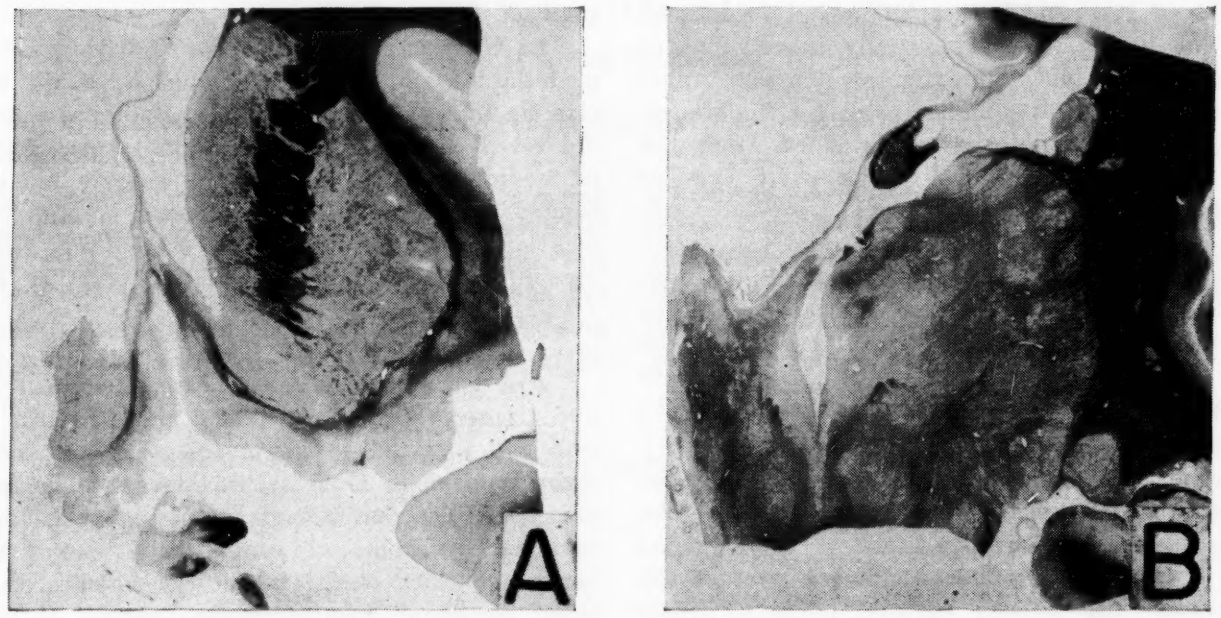


Fig. 1

Figure 1 and C are Weigert transverse sections through the intact left strio-pallidum showing attached remnants of the right basal midline structures. In C, A is **nucleus accumbens septi** and remnants of **area olfactoria**; O is the degenerated remnant of the right optic tract. B and D, through the thalamus, show remnants of the right midline thalamus. The attached fragment in D, which lies in the position of the left medial pulvinar, is largely necrotic tissue.

was covered by a necrotic-appearing membrane. Neither amygdala, hippocampus, nor strio-pallidum could be identified.

After photography the gross specimen was reduced to the size of the basal ganglia and brain stem and cut into 3 frontal slices. These included the entire left strio-pallidum and thalamus with the attached remainders of the right diencephalon and subcallosal cortex. The blocks were cut serially in celloidin at 40 μ, pairs of sections approximately 0.5 mm. apart being stained by Weil's method and by thionin respectively. The complete series extended from the anterior horn of the left lateral ventricle to the caudal end of the nucleus ruber. The detached cortical fragments mentioned above were cut separately and identified as gliosed cortex. The brain stem was also divided into transverse blocks and sectioned with the cerebellum. Blocks through the caudal level of the inferior olive and the decussation of the pyramids were stained by Bodian's method to estimate the remaining fiber content of the right pyramid.

Unless otherwise specified the components of the left basal ganglia appeared normal in sections. The septum pellucidum was grossly intact on the right, as was the mesial subcallosal cortex and a part of the gyrus rectus. The related *radiatio corporis callosi* (Riley 1943) was pale-stained in Weigert preparations but contained some remaining intact fibers. Corresponding to the normal appearing left fornix in Weigert sections there was a sparse distribution of myelinated fibers remaining upon the right side of the septum. A small tissue mass, including parts of the *nucleus accumbens septi* and of the *area olfactoria*, remained upon the right side (fig. 1A) and a few fibers of the anterior commissure penetrated it. The right side of the hypothalamus, forming the wall of the anterior part of the IIIrd ventricle, was intact but quite thin, and attached to it was the completely degenerated right optic tract (fig. 1B). An area of old secondary degeneration joined the normal appearing left uncrossed portion of the optic path, forming the chiasm. Scattered cells were evident in the right hypothalamus, and in Weigert sections pale blue fine striations indicated some remainder of myelinated axons.

The right thalamus was entirely absent except for the midline part just rostral to the mesencephalic junction (fig. 1C and D). Here scattered cells lay medial to the right habenulo-peduncular tract; none were discerned lateral to it. The rostral end of the right lemniscus systems formed the remainder of the nubbin of ''thalamic'' tissue mentioned above. The right habenula was evident.

The cell laminae of the left lateral geniculate nucleus showed transneuronal degeneration of laminae 1a, 2b, and 3b. This confirms Minkowski (1919) and LeGros Clark (1932) who stated that these laminae receive the crossed component of the optic tract.

In Weigert preparations the right pyramid of the medulla was much shrunken and appeared to contain no intact fibers. However, Bodian preparations did reveal a few clusters of normal appearing axons of medium to small size. These were indeed a small component of the much shrunken pyramid, but are mentioned because Brodal has stated that there are ascending fibers in the pyramidal tract of the cat (1952).

SUMMARY

A brief survey is given of the clinical history and of the principal anatomical findings in a woman who had survived 11 years following the loss of a right hemisphere from natural causes. The case has particular neurophysiological interest because of a thalamic syndrome of unremitting pain upon her hemiplegic left side, and other evidence that she could recognize painful stimuli there. In the absence of thalamic relay and association nuclei, and with no appreciable remainder of the midline thalamus, it is hypothecated that the recognition of pain could only have occurred by paths leading to the homolateral thalamus, or alternatively in the brain stem reticular substance.

REFERENCES

BRODAL, A. and WALBERG, F. Ascending fibers in pyramidal tract of cat. *Arch. Neurol. Psychiat.*, Chicago, **1952**, *68*: 755-775.

GUTIÉRREZ-MAHONEY, C. G. The treatment of painful phantom limb by removal of post-central cortex. *J. Neurosurg.*, **1944**, *1*: 156-162.

LEGROS CLARK, W. E. A morphological study of the lateral geniculate body. *Brit. J. Ophth.*, **1932**, *16*: 264-284.

MINKOWSKI, M. Ueber den Verlauf, die Endigung und die zentrale Reprasentation von gekreuzten und ungekreuzten Sehnervenfasern bei einigen Saugethieren und bein Menschen. *Schweiz. Arch. Neur. Psych.*, **1919**, *6*: 201-252.

PIORRY, M. Leçon de Physiologie Pathologique. Destruction de l'hémisphère droit du cerveau, hémiplégie du côté gauche du corps, intelligence intacte. *La Lancette Française*, **1829**, *1*: 120.

RILEY, H. A. *An Atlas of the Basal Ganglia, Brain Stem and Spinal cord.* The Williams Wilkins Company, Baltimore, **1943**, pp. 708.

Reference: WEISS, S., LEVY, I., SMITH, D. and O'LEARY, J. L. Loss of right hemisphere due to natural causes. *EEG Clin. Neurophysiol.*, **1956**, *8*: 682-684.

TECHNICAL NOTES

Editor for Western Hemisphere and Far East, J. KNOTT, Iowa City, Iowa, U.S.A.
Editor for Europe and Middle East, H. SHIPTON, Bristol, England

A SIMPLE ANTI-BLOCKING DEVICE

CARL BAUMANN, BIRGER R. KAADA, M.D. and KRISTIAN KRISTIANSEN, M.D.
Oslo City Hospital (Ullevaal), Norway

(Received for publication: April 6, 1956)

Due to amplifier blocking and excessive pen swing the electrical activity of the brain immediately after electrical stimulation is very difficult to record. This is particularly the case when a strong stimulus has to be applied to a cortical point close to the recording electrodes, for example to produce electrical after-discharges. A device has been suggested to eliminate these disturbances to enable immediate and uninterrupted electroencephalographic recording. The method has proved of particular value in electrocorticography combined with cortical stimulation in epileptic patients.

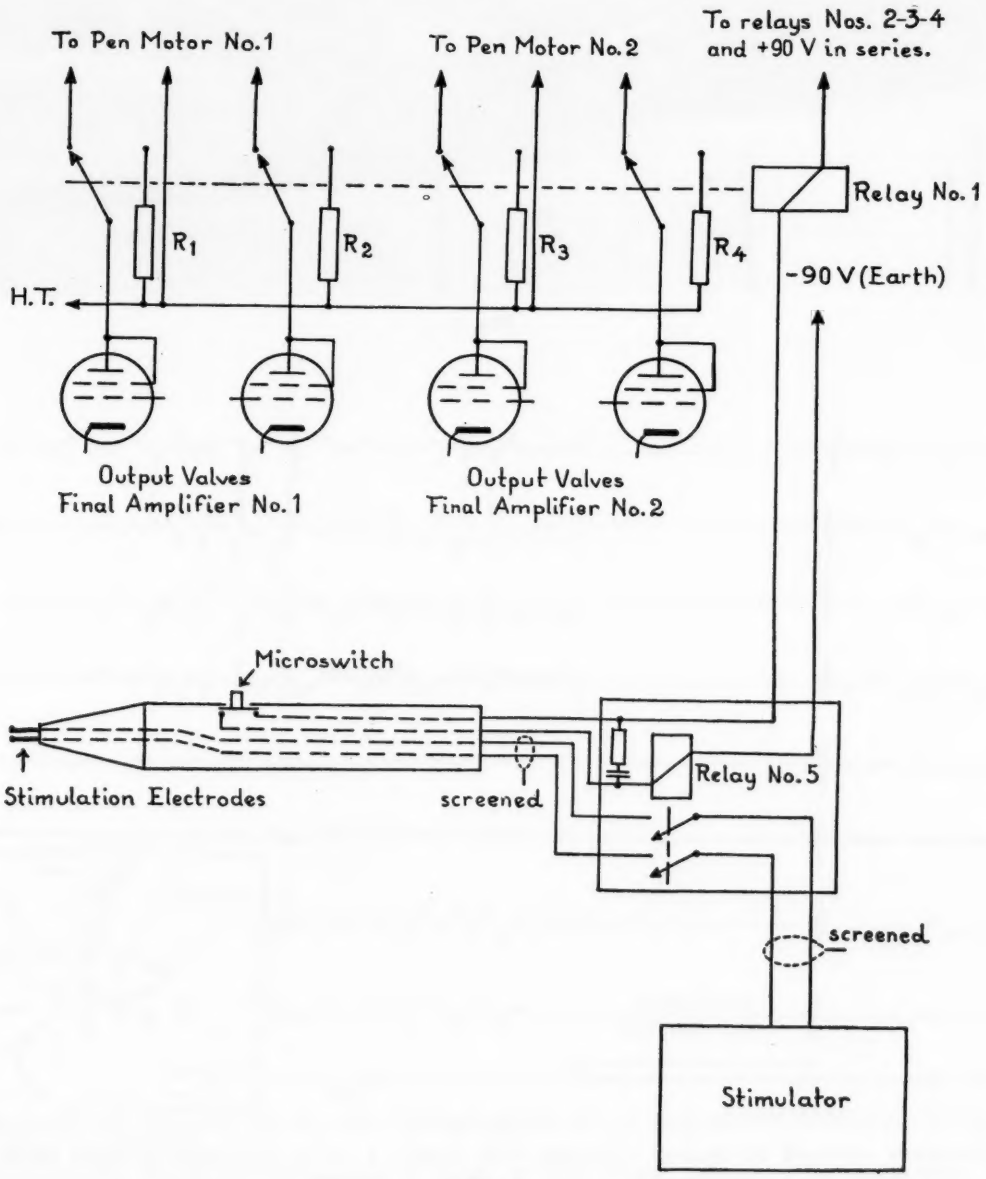


Fig. 1
Diagram of the anti-blocking device (showing two channels only).

The device was originally installed in an Ediswan eight-channel electroencephalograph Mk. II, but can probably be adapted to any other type of EEG-apparatus with slight modifications only. The principle of the device is as follows:

Preliminary tests proved that no interference should be made with the input unit and the pre-amplifiers. Short-circuiting the amplifier inputs during stimulation introduced additional blocking, probably due to slight grid current in the input valves as

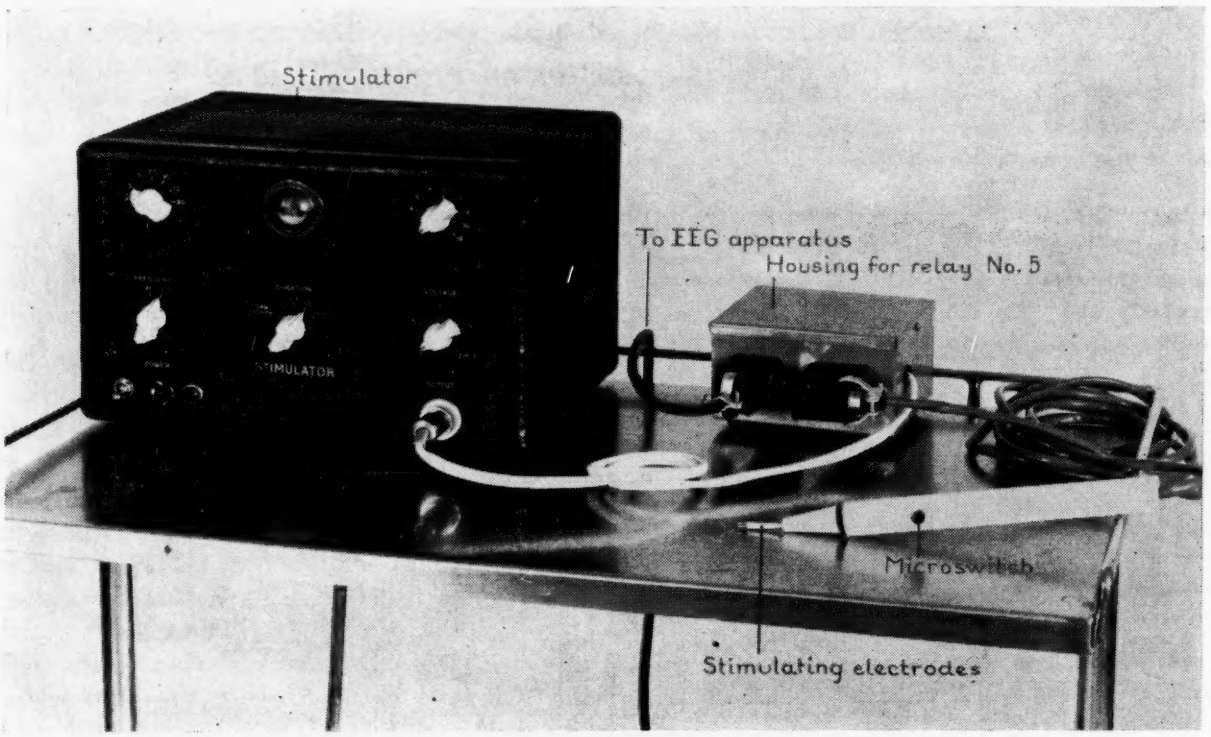


Fig. 2

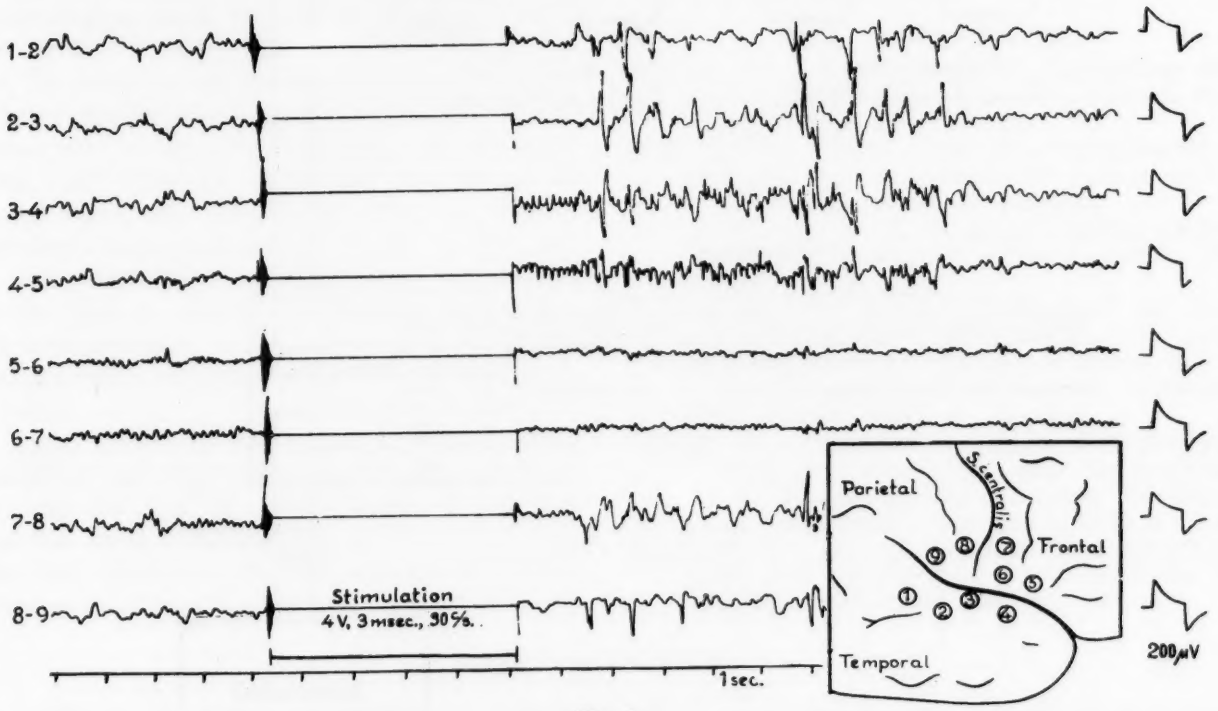


Fig. 3

Electrocorticogram obtained by bipolar recording from points 1 - 9 as indicated on inset at lower right. Electrical stimulation of a cortical point close to point 4 induces an electrical afterdischarge at the adjacent electrodes. No blocking of the amplifiers. Stimulus parameters: 4 V., 3 msec., 30 c/sec., saw-tooth waves.

well as polarisation (despite the use of silver-chlorided electrodes).

In view of the excellent discrimination against inphase signals it was then assumed that blocking might be prevented if the input balance was carefully adjusted. It would then be necessary, however, to modify the output circuit in order to prevent excessive pen swing during stimulation. Five relays were installed, 4 switching the anodes of the power amplifiers to resistive loads (R_1-R_4) during stimulation, the fifth one disconnecting the stimulator during the same period (fig. 1). The 4 relays, wired in series, were connected to the 90 volts DC available from the power pack of the EEG-apparatus. They were controlled by a small microswitch fitted into a specially made stimulator electrode handle as shown in the diagram (fig. 1) and in the photograph (fig. 2). The stimulator relay (No. 5) as well as a small condenser and resistor for spark suppression were mounted in a small box, and the various units interconnected by multiplugs (fig. 2).

As can be seen from figure 3 the pen recorders are inoperative during stimulation. Blocking is almost completely absent, even when stimulating a cortical point close to the recording electrodes and irrespective of whether the bipolar or the monopolar average recording technique of Goldman (1950) is employed.

It should be noted that the single pen swing at the end of stimulation is caused by the particular type of relay which was available. One pair of contacts was operated by the closing of the other pair, thus introducing a short time delay between the closing of the two pairs. A perfect record may be obtained by using standard fast-action type telephone relays.

SUMMARY

A simple device has been suggested to eliminate the blocking of the amplifiers and the excessive pen swing immediately after an electrical stimulus is applied close to the recording electrodes. The method has proved of particular value in electrocorticography associated with cortical stimulation in epileptics.

REFERENCE

GOLDMAN, D. The clinical use of the "average" reference electrode in monopolar recording. *EEG Clin. Neurophysiol.*, **1950**, *2*: 209-212.

Reference: BAUMANN, C., KAADA, B. R. and KRISTIANSEN, K. A simple anti-blocking device. *EEG Clin. Neurophysiol.*, **1956**, *8*: 685-687.

ANOTHER SIMPLE METHOD FOR THE SIMULTANEOUS CINEMATOGRAPHIC RECORDING OF THE PATIENT AND HIS ELECTROENCEPHALOGRAM DURING SEIZURES

L. F. Stewart, M.D., H. H. Jasper, M.D. and C. Hodge
Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute, Montreal

(Received for publication: April 18, 1956)

Only brief mention of other possible methods for accomplishing the purpose set forth in the title will be made, as a thorough review of these is to be had in the communication to the Third International Congress of Electroencephalography made by Schwab, *et al.*

Split Framing.

(1) This involves the photographing of the patient on one half of the film with the other half masked out. The film is then wound back to the beginning (a camera with a frame-counting device must be employed) and the EEG run through the machine a second time from beginning (which must be accurately marked) to end, out of contact with the pens, while it is photographed on the unexposed side of the film, the exposed side now being masked.

Dual Camera Method.

(2) The two events may be photographed simultaneously by two separate cameras, the resulting films being lined up and then rephotographed on a third film for presentation.

Epidiascope Method.

(3) One may project the EEG as it is being run, with an epidiascope onto a screen placed in the camera's field beside the patient.

Television Method.

(4) Television equipment (two cameras) may be employed by means of which the images of the patient and his EEG may appear side by side on one receiver, from the screen of which they may be photographed.

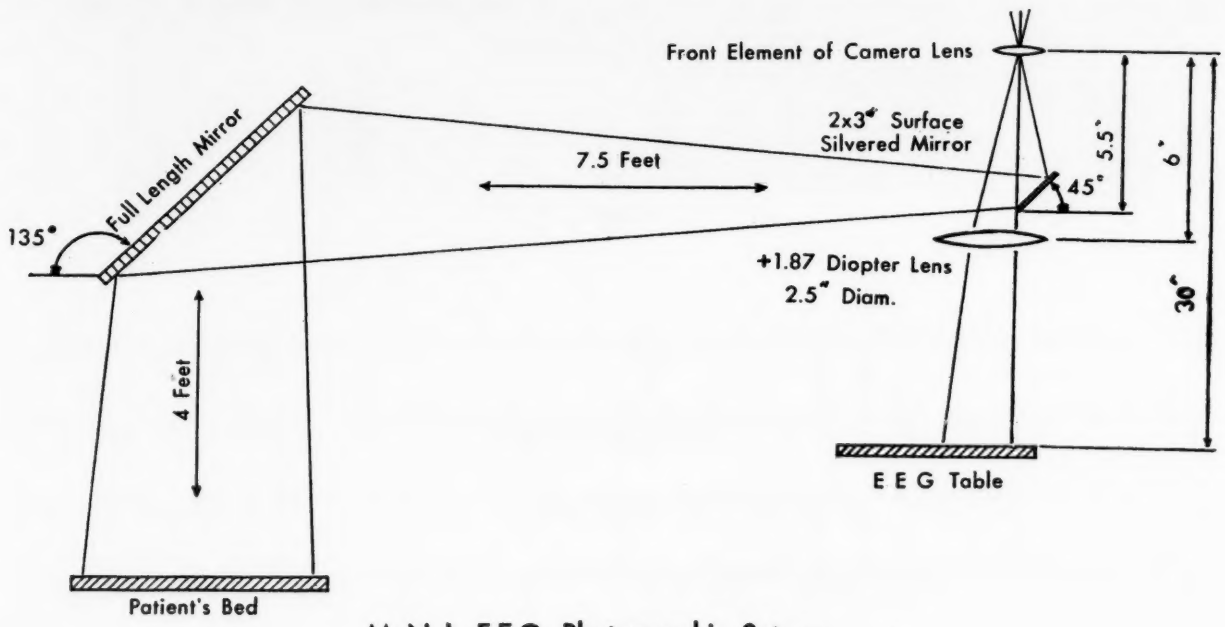


Fig. 1
M.N.I. EEG photographic set-up.

Mirror Splitting Method.

(5) The method of Hunter and Jasper by means of which the image of the EEG trace is projected through a system of lenses and mirrors on to a mirror placed beside the patient in the camera's

field is a technique of which the present method is a modification.

Prism Splitting Method.

(6) The method of Schwab, in which a stereo-attachment is placed over the lens of the camera, one half of this containing a portrait lens while the aperture of this half is over-hung by a mirror which looks down on the EEG record, is the most convenient of those mentioned. The second half of the attachment is focused directly on the patient.

In the present method, the camera is positioned vertically over the EEG table and the record photographed normally through a portrait lens placed some 6″ in front of the camera lens. A small, surface-silvered mirror is interposed between the camera lens and the portrait lens, with its lower edge just above the latter and protruding about half-way into the camera's field. The surface-silvered mirror faces a second, full length, plain glass mirror positioned over the patient, with its long axis parallel to that of the patient, the two mirrors being at the same height above the floor. The large mirror is inclined toward the small at an angle of 45°, and the small mirror is inclined away from the large at the same angle.

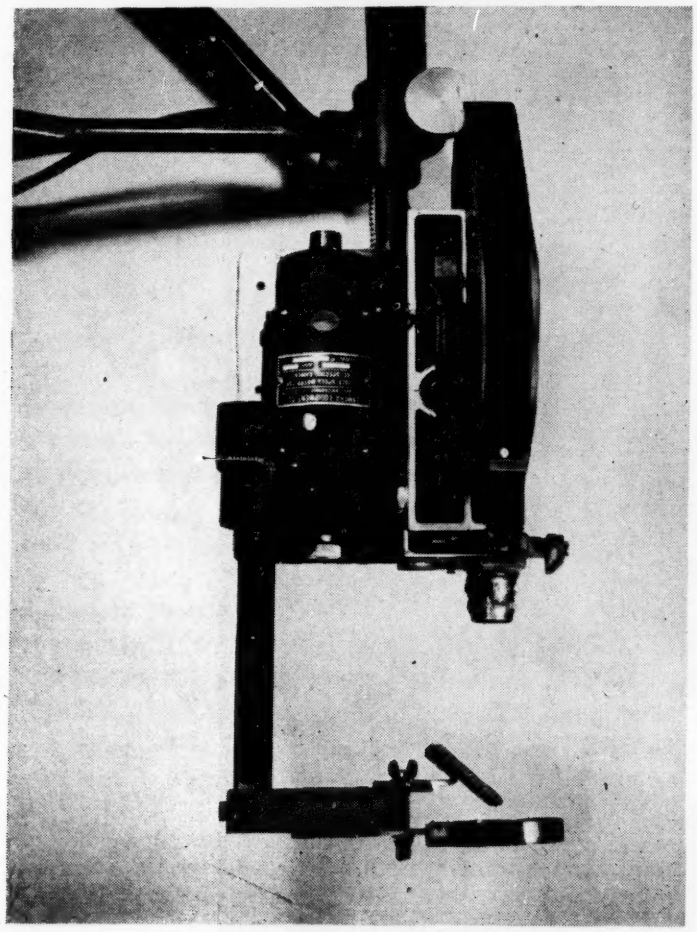


Fig. 2
The photographic recording apparatus viewed from the side.

In this fashion, light entering the left half of the camera lens through the portrait attachment records the image of the EEG on one half of the film.

Light entering the right half of the lens from the patient, via the two mirrors, records the image of the patient on the other half of the film.

The camera is focused for that distance which light has to travel in reaching it from the patient after it has been placed at the requisite height above the EEG table to take in the number of channels desired. A portrait attachment of sufficient power to bring the record into focus for the camera at this distance when the latter is focused on the patient is then selected. This lens must be of sufficient diameter to include all light rays passing from the record to the lens of the camera when the portrait lens is at a point about 6″ in front of the camera lens.

By this method, optical confusion is avoided at the junction on the film between the EEG and patient images, because that part of the bottom edge of the mirror which splits the field is seen by the camera as a line of extreme thinness (the surface of the mirror being square with its edge), and though this line is ''blurred'' out of focus by being so near the camera lens, since it has little dimension of width the ''blurr'' itself remains narrow.

When the film is projected, the patient, viewed from above, appears in normal relationship on the right half of the screen and the EEG, also in normal relationship and moving in the accustomed direction, appears on the left half of the screen.

Light for the patient is supplied by three 150W Mazda projection spots and the record is illuminated by an ordinary 200W bulb in a reflector covered by a spun glass diffusion screen.

All lights and the camera motor are plugged into a modified colortran converter unit.[1] When the lights are plugged into the unit they burn at their ordinary rating, but when the relay is closed which throws the unit into action, the light filaments are over-loaded to burn at a color temperature of 3400°K. and the camera motor is started.

As our apparatus is set up, only the center 6 of the 8 channels on the EEG are photographed. The set-up could easily be altered to take in all 8 channels by elevating the camera higher above the table and using a weaker portrait lens. Of course the individual lines of the trace would then be smaller.[2]

---

1 Made by Colortran Converter Co., 7045 Romaine St., Los Angeles 38, Cal.

2 Surface silvered mirrors, 2 x 3″, are obtainable from the Bosch and Lomb Optical Co., Rochester, N.Y.

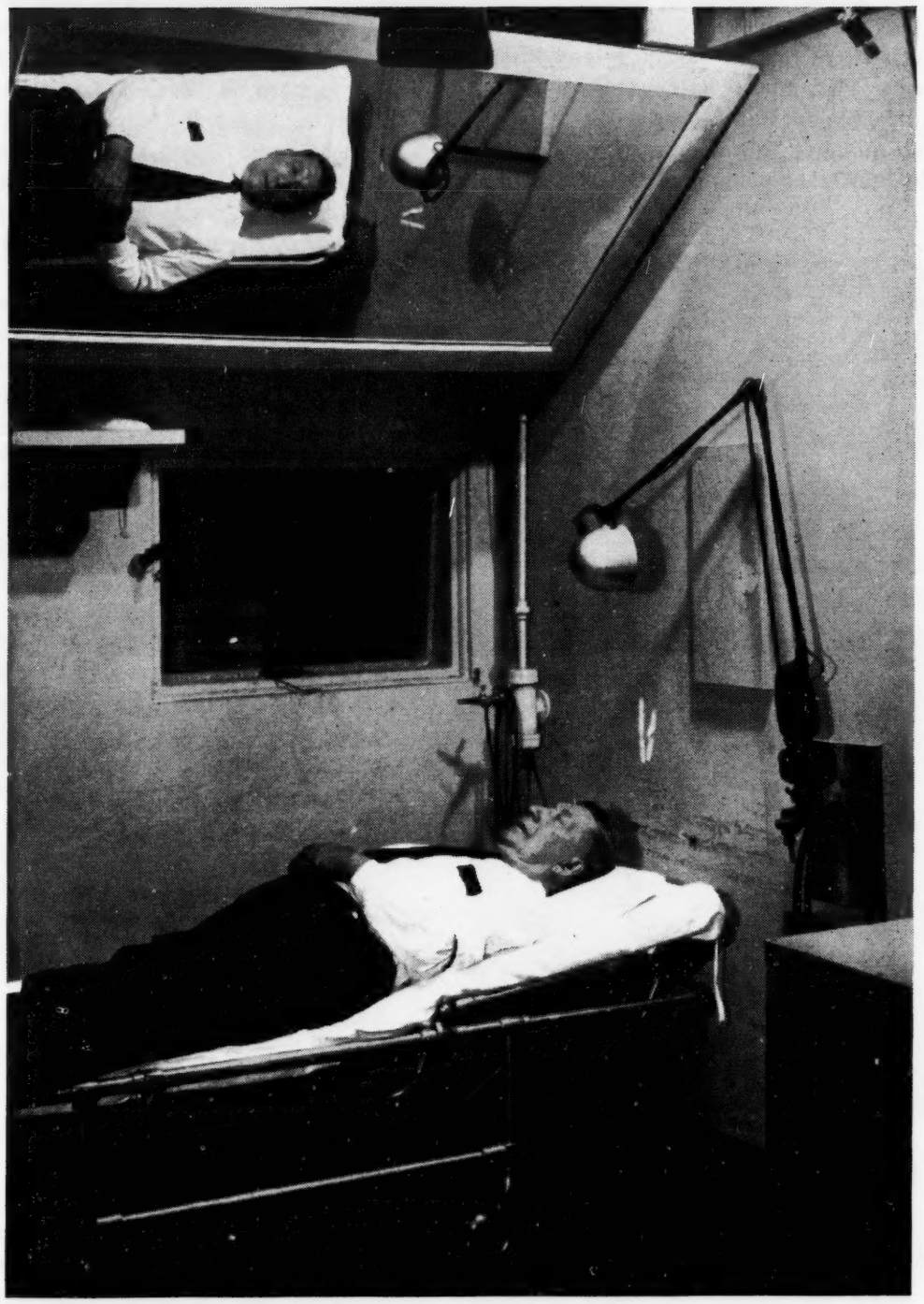


Fig. 3
The position of the patient at the time of photographing.

The portrait attachment can be made at a cost of a few dollars by any optician. It can be on a plain or double convex base and need not be color-corrected because of its low power. It should be 2½" in diam. to duplicate that used by us.

We employ the Kodak Ciné Special Camera driven by a variable speed, synchronous electric motor.[1]

The distance from the end of the camera lens mount to the bottom edge of the mirror is 5½". To the portrait lens, it is 6". The distance from the camera to the patient, through mirrors, is about 11. The height of the camera above the EEG table is 30".

This method combines economy and simplicity with good technical results. It is adaptable to any make or model of camera without the purchase of additional accessories from the manufacturer.

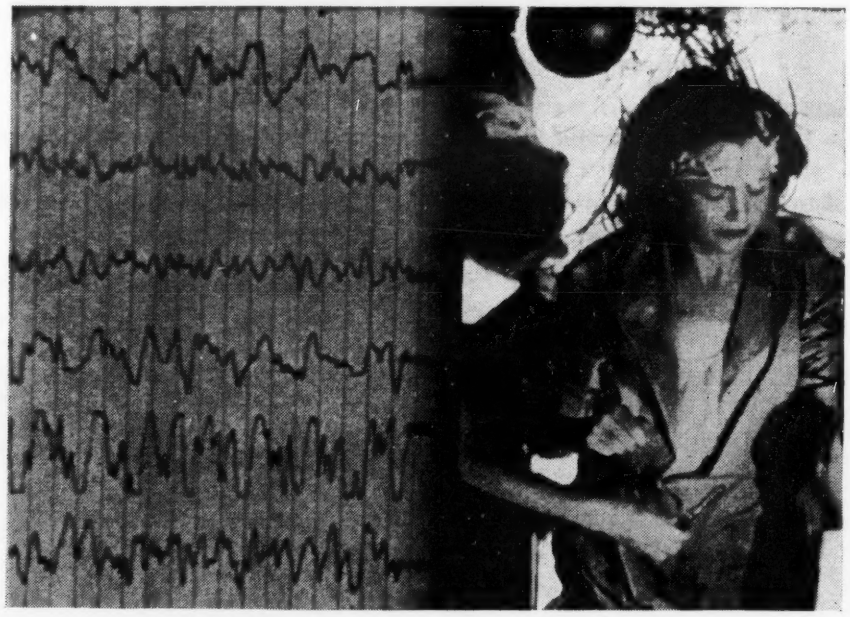


Fig. 4
Appearance of the resulting film as it is projected on the screen.

1 Made by the Camera Equip. Co., 1600 Broadway, N.Y.

REFERENCES

HUNTER, J. and JASPER, H. H. A method of analysis of seizures pattern and electroencephalogram — a cinematographic technique. *EEG Clin. Neurophysiol.*, **1949**, *1*: 113-114.

SCHWAB, R. S., SCHWAB, M. W., WITHEC, D. and CHOCK, Y. C. Synchronized moving pictures of patients and EEG. *EEG Clin. Neurophysiol.*, **1954**, *6*: 684-686.

SCHWAB, R. S., SCHWAB, M. W., WITHEC, D. and CHOCK, Y. C. Synchronized moving pictures of patient with his EEG. *Proc. III Internat. EEG Congress*, **1953**, p. 47.

Montreal Neurological Institute. Reprint No. 538.

Reference: STEWART, L. F., JASPER, H. H. and HODGE, C. Another simple method for the simultaneous cinematographic recording of the patient and his electroencephalogram during seizures. *EEG Clin. Neurophysiol.*, **1956**, *8*: 688-691.

STORAGE OF SILVER CHLORIDE ELECTRODES

R. Cooper, Ph.D.
Burden Neurological Institute, Bristol

(Received for publication: April 6, 1956)

Recent developments in D.C. amplifiers for EEG recordings have shown some shortcomings of silver chloride electrodes (''Monopods'').

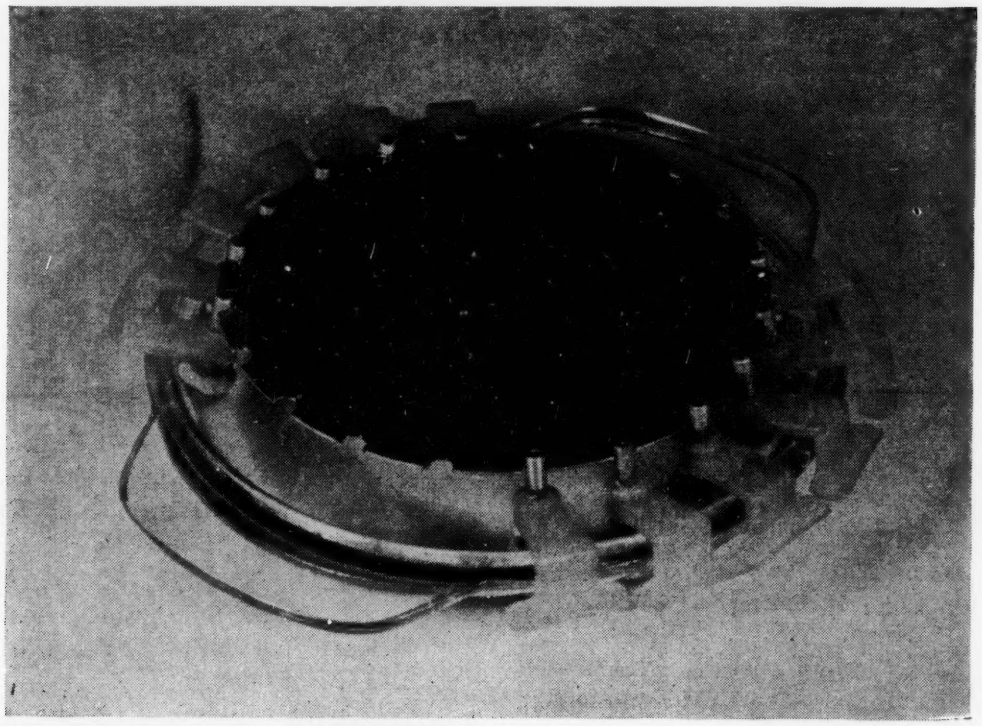
In use these electrodes showed residual potential differences which varied for a period of time several minutes after recording commenced, necessitating continual re-balancing of the amplifiers.

In order to avoid this, electrodes at this Institute when not in use are kept in a separate dish.

Whilst in this dish electrodes rest with their terminals in contact with the periphery of a circular stainless steel plate, their pads being immersed in standard salines. This short circuiting of all terminals maintains the electrodes at the same potential.

Additional to this the stainless steel plate is supported by a central carbon rod the base of which is fixed to the bottom of the dish and immersed in the saline. Since carbon is electro-negative with respect to silver in saline, a cell is formed which continually chlorides the electrodes. The current passing through the electrodes is very small (order of micro-amperes) and is always of correct polarity.

It has been found that the regular use of this device contributes to the achievement of stable and consistent recordings.



Reference: Cooper, R. Storage of silver chloride electrodes. *EEG Clin. Neurophysiol.*, **1956**, *8*: 692.

A COUPLING CIRCUIT FOR THE BICKFORD INTEGRATOR

JOHN DEGELMAN

National Veterans Epilepsy Center, Boston V. A. Hospital, and
Department of Biology, Boston University, Boston, Mass.

(Received for publication: February 21, 1956)

In the investigation by Forbes *et al.* (1956), reliance was placed on the integrating feedback system devised by Bickford (1950) for automatic control of anesthesia. The system worked admirably for its intended purpose but, due to low-impedance shunting in the preamplifier output, the EEG record was distorted. To correct this limitation, a coupling circuit was introduced, as described in the following note.

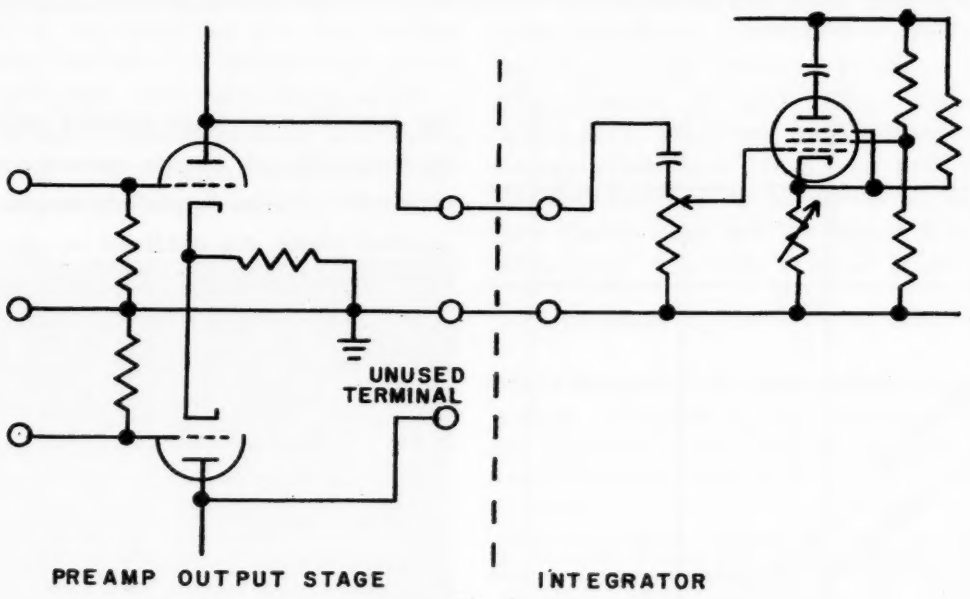


Fig. 1

Connection of preamplifier output to Bickford integrator. Only two terminals of amplifier output are used.

The connections between the preamplifier and the integrator made according to Bickford's specifications are shown in figure 1. The coupling circuit introduced is shown in figure 2. The connections were made from the final plates of the preamplifier of a Grass clinical EEG recorder. These plate potentials were approximately 45 V., making possible direct coupling from the plates to the grids of a pair of cathode followers using a single 6SN7 twin triode. This arrangement was advantageous for two reasons: (1) the EEG output was led off from the preamplifier without distorting the signal, of particular importance when there was need for an undistorted record of the brain potentials from the channel used to control anesthesia; (2) the output terminations of the cathode followers were low-impedance sources well suited to the operation of diode rectifiers. The purpose of full-wave rectification was to give equal emphasis to both the positive and negative portions of the wave, thus to make use of both halves of the preamplifier output. Using the three-terminal output also gave noise cancellation, particularly of rectified A.C. ripple due to the plate power supply.

To test the integration of the apparatus, 50 μV. square pulses were applied to the input of the EEG preamplifier. Since this is nonconductively coupled between stages, the square waves are approximately differentiated and appear to both the integrator and

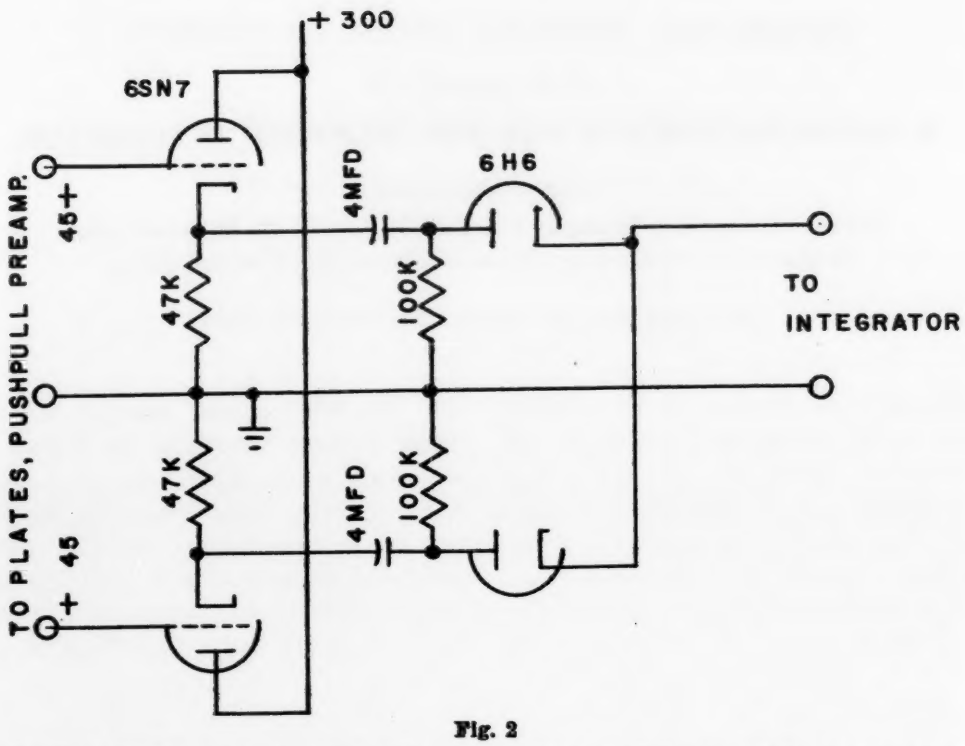


Fig. 2

Coupling circuit used to transform 3-terminal output of EEG preamplifier to 2-terminal input of integrator.

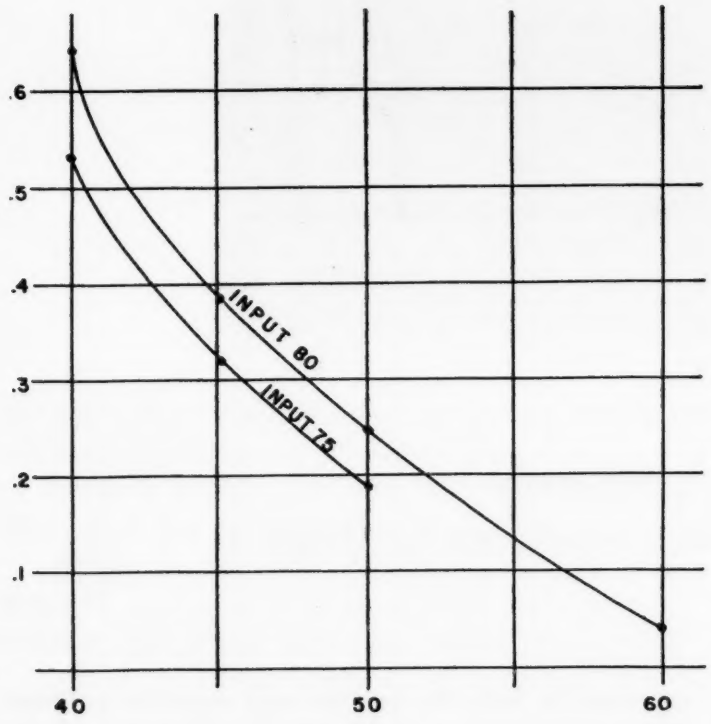


Fig. 3

Abscissae, cathode bias resistor settings; each unit on dial equals 100 ohms. Ordinates, ratio of integrator responses to 50 μV. calibration pulse. In upper curve, integrator input (sensitivity control) set at 80 per cent, in lower curve at 75 per cent.

the inkwriter as steep-fronted pulses that trail off exponentially at a rate corresponding to the time constants of the applied stages. Two pulses, of opposed phase, are obtained — one when the calibrating voltage is applied to the input and the second upon interruption. With all other controls held constant (amplifier gain controls, band pass adjustments, etc.), a series of 50 μV. pulses was applied to the input of the preamplifier for various settings of the integrator bias resistor. The ratios of resulting integrator responses (''clicks'') to calibration impulses (input) were plotted as a function of the integrator bias resistor settings (fig. 3).

The calibration of the apparatus was made by Dr. Alexander Forbes.

REFERENCES

BICKFORD, R. G. Automatic electroencephalographic control of general anesthesia. *EEG Clin. Neurophysiol.*, **1950**, *2*: 93-96.

FORBES, A., MERLIS, J. K., HENRIKSEN, G. F., BURLEIGH, S., JIUSTO, J. H. and MERLIS, G. L. Measurement of the depth of barbiturate narcosis. *EEG Clin. Neurophysiol.*, **1956**, *8*: in press.

Reference: DEGELMAN, J. A coupling circuit for the Bickford integrator. *EEG Clin. Neurophysiol.*, **1956**, *8*: 693-694.

DEUX PROCÉDÉS DE MODULATION DE LUMINOSITÉ DU SPOT POUR L'OSCILLOGRAPHIE CATHODIQUE DE POTENTIELS BIOÉLECTRIQUES [1]

JEAN CERF,[2] M.D. et CHARLES LIBERT
Laboratoire de Pathologie Générale, Faculté de Médecine,
Université de Bruxelles, Belgique

(Received for publication: April 15, 1955)

La photographie de la trace représentative de phénomènes transitoires rapides sur l'écran fluorescent de l'oscillographe cathodique est parfois difficile. L'enregistrement de potentiels bioélectriques brefs, surtout lorsqu'il sont observés à balayage relativement lent de l'oscillographe, pose un réel problème pour l'électrophysiologiste. Les déflexions rapides accélèrent fortement la vitesse d'inscription du spot et déterminent une exposition très inégale du matériel sensible; il en résulte une image faible ou amputée du phénomène étudié. Divers artifices photographiques, à l'enregistrement et au développement des oscillogrammes, contribuent parfois à l'obtention de tracés de densité plus uniforme (voir Mansberg 1950).

Dans le but d'éviter ces difficultés techniques, nous avons réalisé un appareil électronique qui augmente l'intensité lumineuse du spot pendant les phénomènes rapides observés. L'appareil comporte deux sections indépendantes (A et B), à indications d'emploi particulières, permettant de moduler la luminosité du tube cathodique selon des procédés différents. La figure 1 en illustre l'utilisation pour la photographie d'oscillogrammes de potentiels d'action d'un nerf isolé.

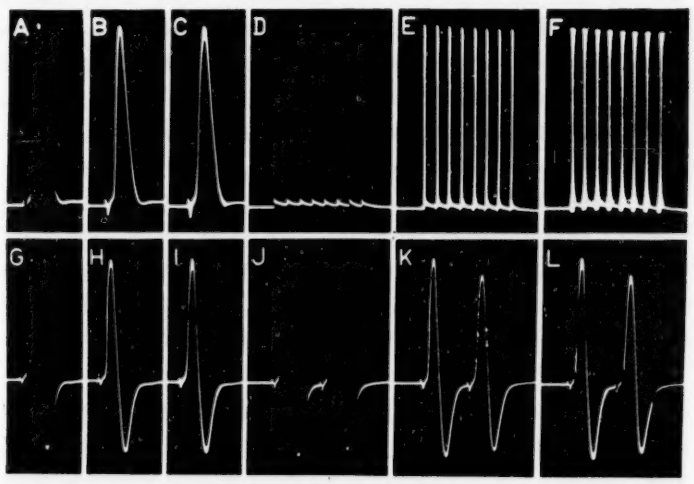


Fig. 1

Renforcement d'intensité du spot, facilitant la photographie de phénomènes bioélectriques rapides sur l'écran d'un oscillographe cathodique.

Oscillogrammes montrant différentes réponses électriques d'un sciatique isolé de Rana temporaria. Stimulation supramaximale pour les fibres du groupe A, par chocs électriques rectangulaires (0,1 msec.), délivrés par étage de sortie HF. Tube cathodique Du Mont 5SP11, filtre bleu. Luminosité du spot ajustée pour l'impression correcte de la trace du balayage, avec ouverture photographique de f: 2,8. Dimension des images sur écran: environ 80 mm. Technique photographique à contraste extrême pour tous les tracés: film Scopix B 35 mm. (blue sensitive), révélateur G 135, papier Document Rapid (Gevaert). Dans ces conditions, les composantes rapides des phénomènes ne s'inscrivent pas sans intensification du spot (voir A, D, G et J).

A et G: potentiels d'action respectivement mono- et biphasique, photographiés sans intensification de la trace. B et H: tracés correspondants à A et G, avec modulation de luminosité par le dispositif différentiateur; noter l'intensification proportionnelle. C et I: tracés correspondants à A et G, avec modulation par le dispositif à impulsion rectangulaire, déclenchée par l'artefact de stimulation et arrêtée à la fin du phénomène; l'intensification sans gradation, par tout ou rien, peut convenir à l'enregistrement de réponses de ce type.

D: courte tétanisation du nerf, sans intensification de la trace. E: idem, avec modulation de luminosité proportionnelle. F: idem, avec modulation par tout ou rien de la luminosité; noter la surexposition relative des pieds et des sommets des potentiels.

J: réponses du nerf à une paire de stimuli, mettant en évidence l'état réfractaire post-réactionnel. K: idem, avec modulation de luminosité proportionnelle. L: idem, avec modulation par tout ou rien de la luminosité. L'intensificateur est déclenché par un voltage supérieur à celui de l'artefact, par réduction de sensibilité; le retard de l'accentuation de la trace est manifeste. La durée de l'impulsion intensificatrice, ajustée sur la réponse conditionnante, s'avère insuffisante pour la réponse réfractaire plus étalée.

DESCRIPTION TECHNIQUE

a) Intensificateur « proportionnel ».

Ce dispositif (fig. 2) applique à la grille du tube cathodique (borne « Z » des oscillographes commerciaux) une tension positive proportionnelle à l'accélération du spot. Etant donné la composante horizontale uniforme du déplacement du spot (balayage selon l'axe des X), on peut démontrer qu'une tension fonction de la vitesse v_Y de deflexion verticale (selon l'axe des Y) répond à la proportionnalité demandée. Une telle tension $T = f(v_Y)$ s'obtient en appliquant $v_Y = \frac{de_Y}{dt}$, e_Y étant l'espace parcouru sur l'écran par le spot (selon l'axe des Y), et t le temps. L'espace e_Y est déterminé par la différence de potentiel entre plaques horizontales de déflexion

---

1 Ce travail a bénéficié de l'aide du Fonds National Belge de la Recherche Scientifique.

2 Chargé de Recherches du F.N.R.S.

de l'oscillographe, proportionnelle au voltage de la transitoire, tandis que la variation de celui-ci au cours du temps fournit le paramètre t.

La tension d'une des plaques de déflexion du tube cathodique n'est pas utilisée pour commander le dispositif, malgré certains avantages que présenterait ce procédé (tension élevée ne nécessitant pas

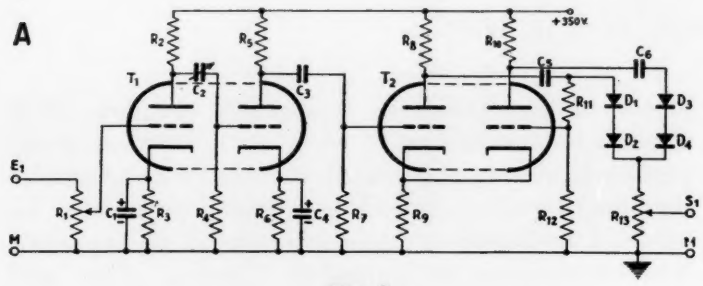


Fig. 2

Section (A) : dispositif différentiateur.

R_1 1M pot, R_2 R_5 R_8 R_{10} 50K, R_3 R_6 R_9 1K, R_4 10K, R_7 R_{11} 1M, R_{13} 250K pot; C_1 C_4 40 μF 50V, C_2 490cm mica var, C_3 0,1 μF, C_5 C_6 0,5 μF; T_1 T_2 6SL7; D_1 D_2 D_3 D_4 1N34.

d'amplification, ajustement automatique de luminosité selon la grandeur d'image); en effet, l'étage de sortie de l'amplificateur vertical (Y) des oscillographes commerciaux fonctionnant souvent en classe AB ou B, le décentrage du spot crée une asymétrie entre tensions plaques du push-pull. Celles-ci, isolément non proportionnelles au phénomène étudié, devraient être recomposées pour représenter correctement le signal d'entrée et être utilisables. La tension de commande est prélevée à l'entrée de l'amplificateur Y de l'oscillographe, ou entre une des deux bornes d'entrée et la masse si l'ampli est symétrique. A ce niveau, le voltage du potentiel bioélectrique étudié est déjà élevé par le préamplificateur qui complète habituellement l'installation. Le signal subit une nouvelle amplification dans le premier étage de l'intensificateur, l'ajustement de R_1 évitant de surmoduler la triode (½ tube 1). La tension obtenue est appliquée à un circuit différentiateur formé par C_2 et R_4. On peut démontrer que la différentiation est d'autant meilleure que RC est choisi petit par rapport à la période de l'harmonique la plus élevée de la tension à dériver (voir Oehmichen 1954). En pratique, la nécessité d'obtenir une tension de sortie suffisante, ainsi que le risque de perturber l'étage précédent par un débit exagéré, limitent la diminution de la valeur de R_4 et indiquent le choix d'une petite valeur pour C_2. La capacité variable C_2 permet d'ajuster le circuit différentiateur à la période du phénomène observé. La perte en tension dans ce circuit est compensée par un second étage à gain élevé (½ tube 1), à la sortie duquel nous disposons d'une tension proportionnelle à la vitesse instantanée $\frac{de_Y}{dt}$ du déplacement du spot selon l'axe des Y. Le signe de la dérivée dépendant du sens du mouvement sur l'écran, cette tension ne peut être utilisée telle quelle pour l'intensification: l'accentuation de luminosité pendant les phases ascendantes des transitoires serait suivie d'un affaiblissement pendant les phases descendantes, ou vice versa. Il est nécessaire de produire une image inversée de la tension dérivée dans un étage déphaseur à 180°, lequel amplifie une dernière fois les signaux (tube 2). Les tensions en miroir obtenues sont recomposées, après élimination des alternances négatives par double redressement dans des diodes au germanium (D_1 à D_4). La tension de sortie, proportionnelle à la vitesse de déplacement du spot selon l'axe des Y et positive quel que soit le sens de ceux-ci, peut atteindre 50 V. et moduler au maximum l'intensité lumineuse du tube cathodique. Le potentiomètre R_{13} permet de prélever le voltage nécessaire à l'intensification parfaite de la trace des transitoires sur l'écran. La luminosité convenant à l'inscription photographique correcte de la trace de balayage est établie par réglage préalable du contrôle d'intensité incorporé à l'oscillographe.

Le cablage est réalisé par connections courtes réduisant les capacités parasites, et le matériel est choisi de qualité haute fréquence. Ces précautions améliorent la réponse du dispositif aux fréquences élevées, et évitent le déphasage, par rapport au phénomène observé, de la tension d'intensification produite. La valeur des condensateurs de liaison C_3, C_5 et C_6 assure une transmission fidèle des signaux.

Ce procédé de modulation intensifie correctement sur l'écran la trace des transitoires (voir fig. 1), et permet l'inscription photographique uniforme de phénomènes bioélectriques les plus divers; il s'impose lorsqu'on désire appliquer l'intensification à l'étude de potentiels complexes ou variables.

b) Modulateur tout ou rien de luminosité.

Malgré ses limitations d'emploi, nous avons retenu pour sa simplicité un autre montage connu en technique oscillographique (Richter 1944), et dont une application à l'électrophysiologie a récemment été décrite par Bonferroni et Mollica (1954). Ce dispositif intensifie par tout ou rien le tracé des phénomènes observés, grâce à l'application momentanée sur la grille du cathodique d'une tension rectangulaire positive de durée ajustable, déclenchée par le potentiel étudié.

Dans une version simplifiée du montage (fig. 3), les impulsions rectangulaires sont produites dans

un étage univibrateur monostable à temps de bascule réglable (double triode T_3). Au repos, la grille de commande est polarisée, par ajustement de R_{14} et R_{15}, à un potentiel légèrement inférieur à celui de la cathode. La triode correspondante se trouve bloquée, et son potentiel anodique est élevé; la seconde triode est conductrice. Un top positif appliqué à la grille

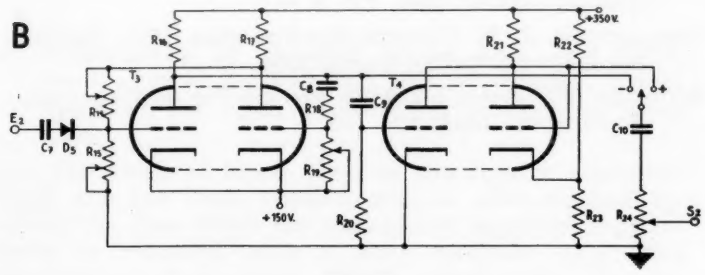


Fig. 3

Section (B) : générateur d'impulsions rectangulaires. R_{14} R_{15} R_{19} R_{24} 1M pot, R_{16} R_{17} R_{23} 25K, R_{18} 500K, R_{20} 1M, R_{21} R_{22} 50K; C_7 500cm, C_8 720cm, C_9 C_{10} 0,5 μF; T_3 6N7, T_4 6SN7, D_5 1N34.

de commande fait basculer instantanément le système, qui revient à sa position d'équilibre initiale après une durée dépendant de la constante de temps du circuit, réglable par R_{19}. La durée maximum atteint 5 msec. avec les valeurs de RC choisies. La tension anodique de la première triode subit une variation négative rectangulaire durant le temps de bascule de l'univibrateur, tandis que l'inverse s'observe à l'anode de la seconde triode. L'impulsion recueillie à celle-ci ne convient pas comme tension d'intensification, les encochages habituels de l'onde rectangulaire positive pouvant créer des variations parasites de luminosité. Il est préférable de prélever l'impulsion négative à l'anode de la première triode et de la rectifier, tout en l'inversant, dans un étage supplémentaire. Celui-ci est un circuit à deux triodes (tube 4), effectuant un double écrêtage par saturation à niveaux différents. Le potentiomètre R_{24} permet de prélever le voltage nécessaire à l'intensification désirée.

Seuls des phénomènes électriques positifs de voltage suffisant appliqués en E_2 peuvent déclencher le mécanisme. Les potentiels bioélectriques doivent être amplifiés pour servir de tension de commande, celle-ci étant d'autre part nécessairement de signe positif. Par différentiation (C_7) et détection (diode au germanium D_5) du signal d'entrée, l'attaque de la grille de commande s'opère exclusivement par un top positif à front raide initié par le phénomène observé, et l'influence de la durée de la transitoire sur la durée de bascule est limitée. Un préamplificateur de signal n'a pas été inclus; le dispositif différentiateur décrit plus haut (section A) en tient lieu, et connecté à la sortie S_1, le montage (B) est actionné indifféremment par de faibles tensions positives ou négatives appliquées à l'entrée E_1. La sensibilité de l'étage univibrateur est ajustée (par R_{14} et R_{15}) afin d'assurer la bascule dès le début du phénomène observé, cet effet résultant également de la différentiation du signal injecté (C_7).

La constante de temps des liaisons par C_9 et C_{10} évite la déformation des impulsions rectangulaires transmises. Dans certains oscillographes, il s'avèrera nécessaire d'augmenter la constante de temps du circuit d'attaque de grille du tube cathodique (entrée « Z »), en renforçant la valeur du condensateur incorporé (à haut isolement). Une liaison insuffisante cause l'extinction du spot à la fin de l'impulsion intensificatrice, par négativation transitoire de la tension appliquée à la grille du tube cathodique.

Ce procédé de modulation présente le défaut d'accentuer sans gradation la luminosité du spot (voir fig. 1); mais la simplicité du montage lui confère une réelle utilité lorsque les observations portent sur des phénomènes bioélectriques simples, de durée et d'amplitude stables. Il s'applique mal à l'étude d'une activité électrique complexe ou d'allure imprévisible. Lorsque le potentiel étudié est précédé d'un artefact de stimulation, celui-ci peut déclencher prématurément l'impulsion intensificatrice. Cet inconvénient constitue une contre-indication à l'emploi de ce dispositif pour l'enregistrement de réponses à grande latence. Lorsque l'artefact est particulièrement réduit, il est possible de limiter la sensibilité du montage à un voltage légèrement supérieur; l'accentuation de la trace du phénomène bioélectrique subira en conséquence un retard manifeste (voir fig. 1, L).

Le même dispositif, déclenché par une base de temps externe, peut délivrer des impulsions rectangulaires négatives éteignant périodiquement le spot à la fréquence donnée, et permet de superposer un signal de temps à l'oscillogramme. Leur forme n'étant pas critique, les impulsions négatives sont prélevées directement à l'anode de la première triode de l'univibrateur.

(L'appareil a fait l'objet d'une démonstration à la Réunion de Bruxelles, le 19 février 1955, de la Société Belge de Physiologie; Cerf et Libert, 1955).

SUMMARY

The paper describes a two-section electronic device for better recording of rapid bioelectric phenomena on the cathode-ray oscillograph screen. In section A (fig. 2), proportional brightening of the trace during transient phenomena is achieved by application of a suitable positive voltage to the cathode-ray tube grid

(Z input). This voltage, proportional to the increase in writing-speed of the spot, is obtained by differentiation of the input signal. In section B (fig. 3), intensity modulation is produced by a positive square voltage applied to the grid. The square pulse is delivered by a one-shot multivibrator, triggered by the phenomenon under observation. This same device, used as a negative pulse-generator driven by an external oscillator, may produce intensity-modulated timing markers which blank the trace at known intervals. The use of either beam-intensifying device described is discussed in the paper.

BIBLIOGRAPHIE

BONFERRONI, P. L. e MOLLICA, A. Modulatore elettronico di brillanza per oscillografia catodica di fenomeni biologici veloci. *Boll. Soc. ital. Biol. sper.*, **1954**, *30*: 733-735.

CERF, J. et LIBERT, C. Modulateur d'intensité de spot pour oscillographe cathodique (démonstration). *Arch. internat. Physiol. Bioch.*, **1955**, *63*: 151-152.

MANSBERG, H. P. Techniques of photo-recording. *The Oscillographer*, **1950**, *12*: 3-16.

OEHMICHEN, J. P. *Circuits électroniques*. Ed. Société des Editions Radio, Paris, **1954**.

RICHTER, W. Beam-blanking circuit for oscilloscopes. *Electronics*, **1944**, *17*: 128.

Reference: CERF, J. et LIBERT, C. Deux procédés de modulation de luminosité du spot pour l'oscillographie cathodique de potentiels bioélectriques. *EEG Clin. Neurophysiol.*, **1956**, *8*: 695-698.

SOCIETY PROCEEDINGS

THE EUROPEAN EEG MEETING

SYMPOSIA ON DRUGS AND ON RECORDING, INSTRUMENTATION AND PROCESSING OF DATA

London, England. May 24-26, 1956

1. Correlation of cerebral blood flow and EEG. — David H. Ingvar and Ulf Söderberg, Nobel Institute for Neurophysiology, Stockholm, Sweden.

The cerebral blood flow of the lightly anaesthetized cat has been studied with a new method by which the flow from the cannulated superior sagittal sinus is recorded with a drop recorder after the elimination of all major diploic anastomoses (Ingvar and Söderberg, *Nature*, **1956**, 177: 339-340). In simultaneous recordings this flow has been correlated with the EEG, the systemic blood pressure and the cutaneous blood flow.

General ''spontaneous'' changes of the EEG, such as the onset of slow waves or high frequency low voltage waves, are accompanied in the lightly anaesthetized preparation by changes — sometimes very large changes — in the cerebral vasomotor tone. It is believed that they represent vivid cerebral vasomotor reactions during changes in the EEG commonly held to represent alterations in the state of wakefulness.

In arousal, ''spontaneous'' as well as induced by natural or electrical stimulation, there is generally an increase of the cerebral blood flow (Ingvar, *Acta. Physiol. Scand.*, **1955**, 33: 169-193) accompanying the electrographic activation pattern. The latency of the circulatory reaction is, however, about two to five seconds. The increased circulation associated with the arousal reaction gradually disappears as the arousal reaction itself passes off.

In the fully anaesthetized state there is a paralysis of the cerebral vasomotor reactions, the cerebral blood flow then being a direct function of the systemic blood pressure. In this state there is also a block of the electrographic arousal reaction upon nociceptive stimulation. In deep barbiturate anaesthesia, for example, there are no cerebral vasomotor reactions observed following nociceptive stimulation and, furthermore, there is no arousal reaction in the EEG which is dominated the whole time by the typical barbiturate spindle activity. During recovery from anaesthesia cerebral vasomotor reactions on stimulation tend to develop at the same time as other autonomic reactions are returning, like those of the pupil and of the nictitating membrane.

Studies have also been carried out on the cerebral blood flow, the EEG, and the systemic blood pressure after administration of drugs most of which have a central nervous action.

2. The effects of intraventricular injections of drugs on the electrical activity of the brain of the conscious cat. — P. B. Bradley and A. J. Hance, Department of Experimental Psychiatry, Medical School, Birmingham.

Adrenaline, 5-Hydroxytryptamine (Serotonin), r-, d- and l-Amphetamine, LSD 25 and Brom-LSD have been injected into the lateral ventricles of the brain in conscious cats by means of an implanted cannula (Feldberg and Sherwood 1953). These animals also carried implanted electrodes (Bradley and Elkes 1953) so that the effects of the drugs both on behaviour and on the EEG could be studied simultaneously.

The normal cortical electrical activity in the unrestrained conscious cat correlates closely with the behaviour state. The EEG of an undisturbed, sleeping cat consists mainly of high voltage slow waves, with occasional bursts of 9-12 c/sec. spindles (''drowsy'' state). Sensory stimuli cause a behavioural arousal and at the same time the slow waves are blocked and fast, low voltage activity at 15-30 c/sec. appears (''alert'' state). As the animal returns to the drowsy state, the EEG may show low voltage, 5-10 c/sec. rhythmic activity for a short period.

Adrenaline (100-200 μg.) and Serotonin (200-250 μg.) injected intraventricularly produced similar effects on behaviour to those described by Feldberg and Sherwood (1954). Whereas adrenaline produced a condition resembling light anaesthesia in which the cat was unable to stand or walk and showed little response to sensory stimuli, Serotonin caused retardation with apparent impairment of co-ordinated movement. The EEG effects with these drugs were not marked and consisted in some cases of an increase in slow activity which could still be blocked by sensory stimuli.

When either of these drugs was followed or preceded by an intraperitoneal injection of amphetamine or LSD 25, the effects of which have been described (Bradley and Elkes 1953b), the behaviour showed little change but the EEG was modified. Thus r-amphetamine sulphate (2-4 mg/kg. intraperitoneally) following intraventricular adrenaline or Serotonin no longer produced hyperactivity, apart from some increase in head movements, although it did establish an alert pattern of fast activity in the EEG. Similarly, LSD 25 (20-25 μg/kg. intraperitoneally) no longer caused alerting of behaviour but in some cases intensified the behavioural effects of intraventricular adrenaline or Serotonin. Instead of producing an alert EEG, LSD 25 caused the appearance of high voltage, rhythmic activity at 4-7 c/sec. which was not localised to a particular cortical area and responded only transitorily to sensory stimuli.

Intraventricular injection of LSD 25 alone (100-200μg.) produced similar high voltage, 4-7 c/sec. rhythmic activity which waxed and waned in amplitude and which again could only be blocked transitorily. The behaviour of the animals was retarded; they showed little interest in their surroundings and rarely changed their position unless handled. Bromlysergic acid diethylamide, which in man does not cause psychological disturbances, produced sedation with a corresponding increase of slow activity when given intraventricularly in doses up to 500 μg; there

was no sign of the high voltage, rhythmic activity peculiar to LSD 25.

r-Amphetamine sulphate intraventricularly had no apparent effect on cortical electrical activity even when as much as 4 mg. was given. Such large doses caused immediate licking and vomiting followed by mild sedation for about one hour. Neither the d- nor the l- isomer had any effect either on EEG or on behaviour in doses of up to 800 μg. intraventricularly.

All these drugs given intraventricularly produced ataxia and sedation in varying degrees, although there were some differences in the EEG effects. In the case of adrenaline, LSD 25 and amphetamine, the effects of intraventricular injections were the opposite to those observed when these drugs are administered by other routes. With Serotonin, Brom-LSD and chlorpromazine (**reported in another communication**) the effects were similar with both intraventricular and intraperitoneal injections.

References :

BRADLEY, P. B. and ELKES, J. *EEG Clin. Neurophysiol.*, **1953**a, *5*: 451-456.

BRADLEY, P. B. and ELKES, J. *J. Physiol.*, **1953**b, *120*: 13P.

FELDBERG, W. and SHERWOOD, S. L. *J. Physiol.*, **1953**, *120*: 3P.

FELDBERG, W. and SHERWOOD, S. L. *J. Physiol.*, **1954**, *123*: 148-167.

3. The effects of chlorpromazine and methopromazine on the electrical activity of the brain of the conscious cat. — P. B. BRADLEY and A. J. HANCE, Department of Experimental Psychiatry, Medical School, Birmingham.

The electrical activity of the brain has been recorded in the conscious, unrestrained cat, using an implanted electrode technique (Bradley and Elkes 1953a). Drugs have been administered intravenously, intraperitoneally and in some cases intraventricularly, in the latter case by means of a previously implanted cannula (Feldberg and Sherwood 1953).

Chlorpromazine, administered intravenously (2-4 mg/kg.) or intraperitoneally (15-20 mg/kg.), caused bursts of irregular 5-8 c/sec. activity to appear in the EEG, together with some slow waves. The animals were retarded and appeared indifferent to the environment and to sensory stimuli. The latter also failed to block the slow wave activity. Animals which were previously friendly or affectionate became indifferent to the presence of the observer, and in a few experiments, appeared somewhat aggressive when disturbed. Similar effects were observed when chlorpromazine was injected into the lateral cerebral ventricles in doses of 0.5-1.0 mg/kg.

Methopromazine was given intraperitoneally in doses of 20-30 mg/kg. With these doses the effects were similar to those seen with chlorpromazine but were less marked. Thus the slow and 5-8 c/sec. activity was often interrupted for long periods by low amplitude, fast activity. The behavioural effects observed with this drug were also similar to those seen with chlorpromazine, but aggressive tendencies were noted more frequently following methopromazine. Owing to the difficulty of dissolving methopromazine in a sufficiently highly concentrated solution, this drug has not as yet been injected intraventricularly.

Both chlorpromazine and methopromazine were also studied in combination with other drugs. These were physostigmine sulphate (0.1-0.4 mg/kg.), atropine sulphate (0.3-3.0 mg/kg.), r-amphetamine sulphate (2-12 mg/kg.) and LSD 25 (10-100 μg-kg.), the effects of which have been described (Bradley and Elkes 1953b). Chlorpromazine given either before or after administration of r-amphetamine or LSD 25 blocked the alerting of electrical activity and behaviour normally seen with these drugs. On the other hand, physostigmine still produced low amplitude, fast electrical activity, when given after chlorpromazine, and atropine produced its characteristic slow wave activity in the EEG in much smaller doses (0.3-0.6 mg/kg.), than those required to produce similar effects in the normal animal (1.5-3.0 mg/kg.). Thus chlorpromazine appeared to potentiate the EEG effects of atropine. Neither physostigmine nor atropine modified the behavioural effects induced by chlorpromazine, however. Very similar effects, both on electrical activity and on behaviour were observed when methopromazine, instead of chlorpromazine, was used in combination with the other drugs.

Chlorpromazine was also studied in acute experiments in *encéphale isolé* and *cerveau isolé* preparation in which blood pressure was recorded simultaneously with electrical activity. In the *encéphale isolé* intravenous injections of small doses (0.5-1.0 mg/kg.) of chlorpromazine were followed by a temporary blocking of the spindle and slow activity characteristic of this preparation. When the slow activity returned, however, it showed an increase in amplitude and greater regularity. These changes could not be correlated with any blood pressure changes which occurred. When larger doses were used only the increase in the slow wave activity was observed, but with doses greater than 4 mg/kg. a marked fall in blood pressure occurred and this was accompanied by flattening of the EEG record. In the *cerveau isolé* no change in the electrical activity was observed following chlorpromazine provided that the transection was complete.

The results of these experiments support the suggestion that the depressant action of chlorpromazine may be due to an action on the brain stem reticular formation (Longo, Berger and Bovet 1954).

References :

BRADLEY, P. B. and ELKES, J. *EEG Clin. Neurophysiol.*, **1953**a, *5*: 451-456.

BRADLEY, P. B. and ELKES, J. *J. Physiol.*, **1953**b, *120*: 13-15P.

FELDBERG, W. and SHERWOOD, S. L. *J. Physiol.*, **1953**, *120*: 3P.

LONGO, V. G., BERGER, G. P. and BOVET, D. *J. Pharmacol.*, **1954**, *111*: 439-450.

4. Action of chlorpromazine, Reserpin and Serotonin on the unanesthetized rabbit's brain (*Cortex, Diencephalon, Rhinencephalon and Reticular formation*). — MARCEL MONNIER and H. GANGLOFF, Laboratoire de Neurophysiologie Appliquée, Geneva.

A stereotaxic method has been developed for electrical stimulation and derivation of the spontaneous or evoked activity of the rabbit's brain (Gangloff and Monnier, *Pflügers Arch.*, *261*, 421, 1955). The technique permits comparison between control and drug effect on the following:

1. The spontaneous electrical activity of the motor, somaesthetic and visual cortex, medial and lateral thalamus, midbrain reticular formation.

2. The threshold and electrographic pattern of the discharge and after-discharge induced by electrical stimulation of the cortical and subcortical structures.

Results :

The drugs, with the exception of Reserpin, induce electrographically an initial relaxation or sleep pattern. This transitory effect is followed, under influence of the three drugs, by a constant long-lasting electrographic alteration, similar to an arousal pattern, but with decreased reactivity to external stimuli and human presence. The voltage of the bilateral spike and wave effects recruited in the cortex by stimulation of the thalamus may be slightly increased, especially by chlorpromazine, and less consistently by Serotonin. On the other hand, the voltage of the spikes evoked in the thalamus and cortex by stimulation of the midbrain reticular formation is decreased by the three drugs, and slightly also the discharge induced in the cortex by stimulation of the rhinencephalon (chlorpromazine and Serotonin). This may be due partially to a decrease of the cortical excitability demonstrated by a marked rise of the threshold of the cortical after-discharge under influence of the three drugs. The passivity and emotional indifference of the animal to external stimuli and human presence may be explained by a disconnection or decreased excitability at this higher thalamo-cortical level. The animal does not sleep however, except perhaps under influence of chlorpromazine, certainly not under influence of Reserpin. It is awake; its EEG shows an arousal pattern, and its reticular system is partially activated, at least in the lower brainstem. In the midbrain, in fact, the effects of the reticular stimulation are rather increased.

Attention or arousal patterns alternate often during the experiment with relaxation patterns, as the expression of an oscillating balance between two functional antagonistic systems: a spike-producing reticular system and a thalamo-cortical recruiting system.

5. A cholinergic "local hormone" mechanism in the cat's brain. — J. E. Desmedt, Laboratoire de Pathologie Générale, Université de Bruxelles, Brussels.

The participation of acetylcholine (ACh) in central nervous mechanisms is still largely a matter for discussion. With respect to the cerebral cortex, it has been shown that small doses of ACh can activate the spontaneous rhythms (Bonnet and Bremer 1937), and that choline esters are liberated within the active eserinized cortex (MacIntosh and Oborin 1953). In the present communication, a case is made for the view that these choline esters may be less concerned with synaptic transmission than with humoral control of cortical excitatory state.

Differentiation between these two possibilities is made difficult by the structural complexity and functional heterogeneity of the cerebral cortex. Nevertheless advantage may be taken of the particular distribution of the two types of cholinesterases (ChE) within the brain (Koelle and others), acetoChE being associated mostly with neurons and butyroChE (or pseudoChE) with neuroglial cells. A combined electrophysiological and enzymological study, using a number of selective inhibitors of these enzymes, gave the rather unexpected result that selective inactivation of butyroChE produces a typical activation pattern of the brain rhythms as well as a behavioural arousal in the sleeping cat (Desmedt and La Grutta 1955).

This result suggests that the neuroglia is effectively participating in the regulation of the chemical milieu of nerve cells, by controlling in some way the level of choline esters within the tissue. The alternative possibility that neuroglial butyroChE would be involved in transmitter processes at the synapses located on neurons somata seems unlikely. On the other hand, the present experimental evidence neither proves nor disproves the possibility that some cortical synapses may be cholinergic and may utilize neuronal acetoChE for the hydrolysis of a transmitter.

The demonstration that neuroglial butyroChE can influence the cortical excitatory state invites consideration of a number of difficult problems. For instance, the physiological substrate of butyroChE is unknown, and one may question whether it is ACh rather than another choline ester; in fact, the optimal substrate for cat's brain butyroChE is butyrylcholine, and it must be remembered that pharmacological assays like those of MacIntosh and Oborin (1953) do not so easily differentiate between choline esters (see Banister, Whittaker and Wijesundera 1953). Also, the locus where the choline esters responsible for the pharmacological arousal are elaborated can only be guessed: they might be secreted like "local hormone" by some neurons or by some neuroglial cells, or they might be released by some afferent fibre system.

Finally, it is puzzling to imagine how this humoral mechanism can be "set" to any particular level if it does indeed participate in the control of the ever-changing cortical excitatory state by regulating local chemical gradients. However, the neuroglial butyroChE might have a more static function, e.g. to prevent the concentration of choline esters from rising above a (fixed) critical level within the nervous tissue.

Reference :

Desmedt, J. E. and La Grutta, G. *J. Physiol.*, **1955**, *129*: 46P-47P.

6. The central action of adrenaline: pharmacological consequences. — P. Dell and M. Bonvallet, Faculté de Médecine, Paris.

Physiological data

Two series of experimental data suggest the existence of an adrenergic component at the mesencephalic and hypothalamic level of the brain stem reticular formations:

A. The ascending reticular system responsible for cortical activation as well as the descending system responsible for the facilitation of the spinal motricity are stimulated by the direct action of adrenaline at their mesencephalic level. Intravenous injection of adrenaline or liberation of endogeneous adrenaline (nociceptive stimulation, splanchnic or bulbar stimulation) in a preparation with a prebulbar section of the brain stem produce an intense activation of the electrical activity of all cortical areas. This effect disappears after an intercollicular section passing to the ventral surface just rostral to the pons. Cortical activation consequently is not due to a direct cortical action of adrenaline but to an action on the mesencephalic portion of the reticular arousal system (Bonvallet, M., Dell, P., Hiebel, G., *EEG Clin. Neurophysiol,*. **1954**, *6*: 119). These results have been confirmed and extended (Rothballer 1955). On the other side, adrenaline produces a considerable facilitation of monosynaptic and, less regularly, of polysynaptic

spinal reflexes in a preparation with a section of the brain stem at the premamillary level. This facilitation disappears after a more posterior section, e.g. prepontine or transpontine section. The facilitatory effects result from the action of adrenaline on the hypothalamic and mesencephalic component of the reticular facilitating system (Dell, P., Bonvallet, M. et Hugelin, A., *EEG Clin. Neurophysiol.*, **1954**, *6*: 599). These results have been confirmed (Sigg, E., Ochs, S. and Gerard, R. *Amer. J. Physiol.*, **1955**, *183*: 419). Light doses of barbiturates destroy these effects.

B. From the chart published by Vogt (*J. Physiol.*, **1954**, *123*: 451) indicating the accumulation of "sympathin" (mainly non-adrenaline) in different parts of the encephalon, it appears that "sympathin" is concentrated predominantly in the brain stem regions overlapping with the sympathetic and somatic reticular systems.

The fact that certain reticular interneurones are directly sensitive to the influence of adrenaline and that there is an accumulation of "sympathin" (liberated *in situ*) at the same central levels suggest the existence of an adrenergic link operating in the reticular function.

Pharmacological applications

These physiological data may be taken as a starting point to explain the central action of drugs structurally related to adrenaline, or known for their sympathomimetic or sympatholytic action at the sympathetic periphery. We have studied in detail d-amphetamine and a compound with adrenolytic effects, chlorpromazine.

A. It has been shown that d-amphetamine has the same EEG arousal effects as adrenaline and that it enhances the central action of circulating adrenaline. These effects are even more powerful: after a postmamillary section of the brain stem there is no more cortical activating effect of adrenaline, but d-amphetamine still acts; this effect is lost however after a premamillary section. We interpret these results as showing that so long as a small quantity of reticular substance remains in relation with the cortex, d-amphetamine may develop its activating action (Hiebel, G., Bonvallet, M., Huve, P., Dell, P., *Sem. Hôp.*, Paris, **1954**, *30*: 1880).

B. Concerning chlorpromazine a depressing action on the reticular systems has been demonstrated; this depression is the result of at least three converging mechanisms; a diminution of responsiveness of R. F. to afferent stimuli, a suppression of responsiveness to circulating adrenaline, an enhancement of the depressing effects of carotid sinus afferences (Hiebel, G., Bonvallet, M., Dell, P., *Sem. Hôp.*, Paris, **1954**, *30*: 2346).

It may be suggested that other drugs of the same series act, partially at least, through the same fundamental physiological mechanism.

7. The action of LSD 25 on the behaviour and on the cortical and rhinencephalic rhythms of the chronic cat. — P. Passouant, Th. Passouant-Fontaine and J. Cadilhac, Faculté de Médecine, Montpellier.

LSD 25 (Sandoz) produces in man changes in mood and perception, particularly in the visual modality. In animals, the effects of the drug on the electrical activity of the brain have been interpreted in various ways.

The relation between the changes in cerebral electrical activity and those in behaviour under the influence of LSD 25, have been studied in 10 chronic cats carrying electrodes implanted at the level of the cortex and various sub-cortical structures, particularly in the rhinencephalon (Cornu Ammonis, amygdala, cingular gyrus and mamillary bodies). The drug was given by intra-muscular injection in doses of 50 to 200 microgram/kg. In most animals successive experiments were made at several days interval. The effects of LSD 25 were compared with those of Reserpine or Serotonine injected either successively or at the same time.

1. *The behaviour* of the animal is little changed with doses below 70-100 micrograms/kg. With larger doses motor agitation and unstable behaviour appear, without marked change in the control of movement, co-ordination or sensory perception.

2, *The spontaneous electrical activity* is greatly altered; the cortex shows prolonged bursts of large slow sinusoidal waves at 3-4 c/sec. similar to those seen in deep sleep. These slow waves appear also in the hypothalamus, the mamillary bodies and in the septum. The activity of the hippocampus on the other hand is little changed.

The cortical responses picked up at the level of the specific projection areas are not affected, but they are masked by the cortical bursts and are seen clearly only in the intervals between these.

3. The electrical thresholds for after-discharges are unchanged by LSD 25, nor is the duration of the after-discharge affected. On the other hand the recovery period for the electrical activity following a cortical seizure is markedly increased.

4. The electrical effects of LSD 25 persist after the injection of large doses of Reserpine or Serotonine, which produce striking and characteristic vegetative and motor changes.

These results demonstrate :

1. The contrast between the clarity of the changes in cortical electrical activity and the slightness of the motor and vegetative manifestations after LSD 25.

2. The lack of correspondence between the effects on the electrical activity of the cortex and on that of the rhinencephalon.

3. The absence of antagonism between LSD 25 on the one hand and Serotonine or Reserpine on the other.

4. Above all, the existence of a selective action of LSD 25 on the regulation of cerebral electrogenesis and on the diffuse projection centres of the cortex. This action explains to a great extent the clinical phenomena seen after exhibition of LSD 25 in man.

8. The action of bulbocapnine on the behaviour and on the cortical and rhinencephalic rhythms of the chronic cat. — P. Passouant, Th. Passouant-Fontaine and J. Cadilhac, Faculté de Médecine, Montpellier.

Bulbocapnine, one of the alkaloids of Carydalis Cava, produces a cataleptic state in animals. This action has been studied particularly by Baruk and de Jong (1930) but its mechanism is still obscure.

A parallel study of the changes in behaviour and cerebral electrical activity after administration of bulbocapnine has been made in 10 chronic cats carrying electrodes implanted at the level of the cortex and various subcortical structures, particularly the rhinencephalon (Cornu Ammonis, amygdala, cingular gyrus, mamillary bodies). The doses of bulbocapnine varied from 20 to 50 mg/kg.

1. The changes in behaviour were invariable; catalepsy with muscular stiffness and maintenance of imposed attitudes are obtained with doses of about 20 mg/kg. Motor reactions produced by electrical stimulation of the reticular formation, the amygdala or the cortex are slowed but not suppressed by bulbocapnine.

2. Cerebral electrical activity on the whole is little changed. However, in most cases the following effects were noted: a reduction in amplitude of the record and sometimes induction of a sleep pattern; quite large short spikes in the hippocampus; an increase in the cortical responses to sound and light stimuli.

3. The electrical thresholds for after discharges are raised, generally in all structures studied, even though the actual duration of the after discharge and the motor and vegetative changes which accompany it remain unchanged. In some cases these thresholds are raised to a greater extent in the cortex and the reticular formation than in the hippocampus.

In conclusion:

1. There is a clear contrast between the striking changes in the behaviour of the animal and the triviality of the modifications in spontaneous electrical activity of the brain.

2. The elevation of excitability thresholds and the induction of sleep patterns suggest a central depressive action for bulbocapnine, but the variations of excitability are so great that no conclusion can be drawn as to the anatomical site of election of the drug.

9. A small 6 channel EEG instrument. — T. J. McDermott, Neuropsychiatric Research Centre, Whitchurch Hospital, Cardiff.

The relatively high cost of present day EEG machines suggested the possibility that the electronic commutator techniques, developed for a 24 channel instrument (McDermott 1954) could be used to design a small inexpensive 6 channel instrument.

The small 6 channel instrument described is intended for use only in centres where the cost of a full-size EEG unit would be prohibitive, for the preliminary selection of patients to be sent to the central EEG unit for full investigation by the usual methods.

The use of the electronic commutator precluded the use of ordinary pen recorders; consequently the display of the 6 channel traces on the face of a cathode ray tube (C.R.T.) was adopted. No permanent record can be obtained from the C.R.T. except by the use of a camera attachment. However a C.R.T. with long after-glow screen is used. The tracing can thus be observed for a sufficient length of time for an estimate of the nature of the EEG record to be made. The electronic commutator enables a minimum number of thermionic valves to be used. One Cascode preamplifier stage is used per channel before the commutator modulators. Unipolar electrode connection with an electrically derived reference potential is used, so that foci can be recognised by the observation of voltage maxima. The six channel traces are deflected horizontally by a repetitive or single-stroke time base which can be run at 1.0 cm/sec., 3 cm/sec. or 10 cm/sec. The channel deflection sensitivity is approximately 1 cm. for 50 μV. with a spot size of 0.3 mm. and maximum deflection of 13 mm., the basic irregularity being of the order of 3-5 μV. r.m.s. The instrument is made in two sections, a display unit 18″ × 12″ × 9″ of 20 lbs. weight, and a power supply 12″ × 9″ × 8″ of 22½ lbs. weight. The total power consumption is less than 150 watts.

10. Problems in the design of a 21 channel transistor EEG machine. — J. A. V. Bates and J. D. Cooper, M.R.C. Unit, National Hospital, Queen Square, London.

The machine under construction is intended for use in detailed EEG and ECG study of a few patients rather than routine investigation of many. It is designed round a writer-unit of 21 pens recording on 9 in. (23 cm.) paper. The EEG trace we are familiar with is based on a 5 cm. radius pen with a 2 cm. peak-peak deflection, and a paper-speed of 3 cm/sec. and a trace width of 0.02 in. (0.5 mm.). In the new unit the peak deflection, paper width and trace speed are all halved. Thus the same proportion is maintained in the record of half normal size, but there is less radial distortion and, what is more important, there is a four-fold reduction in power needed to operate the pen. We have a definite need to keep the machine small and mobile and this, together with consideration of cost and ease of operation, has led us to abandon the conventional idea of multiplication of the unit independent amplifier, and hence to abandon the flexibility which the conventional scheme gives to the operator. We thus have arranged for no independent controls for attenuation, HF cut and LF cut. We also are proposing to have no independent electrode switching, but in its place we have the ability to select a large number of alternative combinations of 42 electrodes and 42 inputs, by the insertion of easily prepared cards into an appropriate "contact" unit. These simplifications and sacrifices, coupled with the use of transistors, enable us to contain the electrical equipment for 21 channels, the writer unit, paper store, and all supply batteries in a space 2 ft. (60 cm.) cubed.

The use of transistors in a high gain physiological amplifier involves at the outset a solution to the problem of the significant variation of their working characteristics with changes in ambient temperature. Offner claims to have solved this by the use of circuits involving mechanical choppers but we did not feel sufficiently confident in the reliability of any available components to follow his lead. We have instead converted the conventional push pull valve circuit to transistor operation, and we are relying on the delicate temperature control of "heat sinks" and a special layout to achieve a constant ambient temperature at the upper limit of the daily swing (80°F, 27°C) in the vital parts of the circuit. This solution brings with it other difficulties in the construction and testing of prototypes and in servicing which must all be done at the same ambient temperature, but two other possible solutions to the problem of temperature instability seemed to present greater difficulties:

1. Cooling to the lower limit of the daily swing (50°F or 10°C) is more difficult to achieve on a small scale than heating and would bring with it problems of water condensation in the equipment.

2. Matching transistors in pairs both for equal gain (to achieve adequate in-phase rejection) and for equal change of current with change of temperature would be quite impracticable at present.

There are two other problems in connection with transistors which are not inconsiderable; firstly, achieving the right condition at the input circuit to obtain both low noise and a reasonably high input impedance — the solution we have adopted is to use

a very low collector current in spite of the fact that this increases the temperature instability; secondly, the problem of obtaining sufficient power from available transistors to drive available pen-writers. This has only been possible to solve by the power economies achieved by a lower pen deflection.

11. Economy of amplifiers for multichannel recording. — H. B. Morton, National Hospital, Queen Square, London.

The need for greater simultaneous EEG coverage has led to the development of apparatus with many pen recorders, each driven by its own amplifier. With the 20 or so recording electrodes commonly used for clinical investigation, a point is reached where the number of input grids exceeds the total number of electrodes. It would appear, therefore, that it might economise in equipment to use a single sided amplifier for each electrode rather than a push-pull amplifier for each pen, as in the conventional EEG equipment.

The adoption of this system of individual electrode amplifiers leads to major changes in the design of apparatus. For instance, the electrode selector switch, normally placed between the electrodes and the input to the amplifiers, may be placed between the amplifier output terminals and the pens, enabling switching to be carried out as a point where the signal level is of the order of volts rather than microvolts. Selection of electrode patterns may then be carried out whilst recording, without blocking the amplifier.

The number of traces available from a given pattern of electrodes would be limited primarily by the pen recorders available, the one assembly of electrode amplifiers serving any number of such recorders.

The use of individual amplifiers for each electrode raises the question of the other input terminal, and the proposal is that each electrode potential is measured against the average potential of all the electrodes on the head (Offner 1950). The output from such an arrangement would be:

1. Normal bipolar recordings, obtainable between amplifier outputs.
2. Unipolar information, available between any amplifier output and an average point.
3. Any combination of both systems, available simultaneously by selection on the electrode switch.

As an electrode amplifier could be connected to any recorder it would be necessary that each amplifier had the same gain and frequency response as that of its neighbours; a machine designed to meet these requirements would be specifically for EEG recordings and not for use as a general purpose physiological amplifier. This leads to a simplification of controls, with the operator faced with only three knobs for control of gain, high frequency response and time-constant.

A multi-channel amplifier designed to test the practicability of associating one amplifier with one electrode has been constructed and its suitability as a clinical electroencephalograph is at present being evaluated. The system of electrode amplifiers selected for the first tests is similar to that described by Lilly (1949), being an extension of the push-pull amplifier principle and utilising a high impedance common to the cathodes of all the electrode amplifiers. This impedance will provide discrimination against in-phase signals on all inputs relative to earth and, at the same time, a signal will be developed across it which is proportional to the average of all the inputs. Hence the output signal from one amplifier will be a measure of the potential difference between the electrode to which it is connected and the average of all electrodes.

The ability of such an amplifier to provide a high "differential gain" (Offner 1947), whilst maintaining both a low "in phase gain" and a low "inversion gain", is one of the factors at present being investigated.

References :

Lilly, J. C. A method of recording the moving electrical potential gradients in the brain. The 25 channel Bavatron and Electro Iconograms. *Proc. Conf. Elec. Inst. Nucl. Med.*, New York, Oct. 31st - Nov. 2nd, **1949**.

Offner, F. F. Balanced amplifiers. *Proc. I.R.E.*, **1947**, *35*: 306-310.

Offner, F. F. The EEG as potential mapping. The value of the average monopolar reference. *EEG Clin. Neurophysiol.*, **1950**, *2*: 215-216.

12. A micrographic oscillograph for EEG and neurophysiological recording. — Claude Leroy, L'Hôpital Psychiatrique de Villejuif, Paris.

The apparatus has 8 channels, providing for EEG recording with direct writers on standard 35 mm. film; this is smoked with lamp black and the record is fixed with cellulose varnish.

The recording speeds are 0.5, 1.0, 2.5, and 5 mm. per sec. driven by a synchronous motor, and 10, 20, 40, 80 and 160 mm. per sec. with a non-synchronous motor. A ninth signal writer is available.

The calibration gain provides 0.5 mm. for 50 μV. input. The frequency response is practically flat from 0 to 800 c/sec.; the amplitude is still up to 60 per cent at 1,200 c/sec., the natural frequency of the movements being 850 c/sec.

The trace thickness is 0.01 mm. The writer length being 37 mm., the arc distortion is much less than with an ordinary EEG recorder. Direct recording in this way of the higher frequencies encountered in neurophysiology is perfectly possible. Storage space required for records is reduced by a factor of 20.

This equipment has been attached to the output of the third stage of an E.C.E.M. type of EEG amplifier with the addition of a special fourth stage, the original power output stage being kept for paper recording.

13. Radio-Electroencephalography. — W. Götze and A. Kofes, EEG Laboratory, University of Berlin, Berlin.

In order to make possible a derivation of brain potential while the subject underwent physical stress, the EEG was transmitted by means of radio waves utilising a method similar to that proposed by Breakell and his colleagues.

The brain potentials are first taken through a carrier-frequency amplifier. The output of this is used to modulate a short-wave transmitter whose frequency is multiplied by a frequency multiplier to approximately 160 M/cycles (2m) and emitted by an aerial. The carrier-frequency (2m) is picked up and amplified in an H. F. amplifier. The next step is a frequency changer producing an intermediate frequency which, through an appropriate amplifier, is further amplified and demodulated to regain the low frequency brain potentials. This provides the input

for one of the channels of a Grass EEG machine for continuous recording.

As a control experiment for the quality of the brain potentials as transmitted by radio and subsequently recorded, the same derivation was recorded simultaneously directly through the Grass machine, in a different channel. Recordings were made with the subject at rest, while overbreathing, and under Evipan. The records obtained via radio transmission and those obtained directly showed close agreement.

The reproduction of alpha, beta and delta waves approximated true frequency and amplitude with a high degree of fidelity.

Transmitting and receiving equipment was arranged for a start in the same room to facilitate comparison of two channels on the same recording machine. However, we succeeded not only in recording brain potentials broadcast in the same room, but also from different storeys of the building such as from the basement to the laboratory on the second floor. Other experiments showed that the transmitter has a reach of 2 km. (1.24 miles). The dimensions of the transmitter and the carrier-frequency amplifier could be arranged so that they could be worn by the subject. There was no effect on the brain potentials due to the close proximity of the transmitter to the subject. Transmission was also carried out with the subject and equipment outdoors. It is, of course, also possible to transmit other biological phenomena such as EKG and muscle potentials.

Investigations of brain potentials under the influence of physical stress are planned.

14. A per cent-time computor and associated band pass filter. — G. W. Morris, Crichton Royal, Dumfries.

This equipment was designed to measure the time during which alpha rhythm was present in the EEG and to express it as a percentage of time. The computation is made and written out at regular intervals as routine EEG recording proceeds.

The rhythm is isolated by means of a band pass filter of a type similar to that previously described by Morris and Dawe. These filters consist of a number of electronic resonant circuits tuned to different frequencies and connected in such a way that their resonance curves overlap to produce a band pass characteristic. Special precautions are taken to minimise the effect of variations in supply voltage and changes in valve characteristics. In the particular application the filter is arranged to pass frequencies of 8 to 13 c/sec.

The output of the filter operates trigger circuits when the amplitude exceeds a certain critical value and thereby switches on a capacitor charging circuit. A timing device is arranged to interrupt the charging should the input cease for more than a very brief interval. Other circuitry delays the commencement of charging until three consecutive cycles have been recorded. After a standard interval of time the capacitor is discharged and the discharge time recorded by time marks on the EEG record at 1/10, 1/2 and 1 sec. intervals. The discharge rate is adjusted so that 10 seconds corresponds to 100 per cent. Both charging and discharging circuits incorporate Miller Integrators to ensure linearity and the capacitors are duplicated so that one may be written out while another is being charged.

The time marker signals are generated by circuits incorporating Dekatrons which count down from the mains frequency of 50 c/sec. Further frequency dividers control the length of the standard charging epoch and the sequence of the various operations.

Although designed for a specific series of experiments to study the organisation of the alpha rhythm in relation to age and psychiatric treatment, this apparatus could be of assistance whenever the time pattern of any rhythmic activity is being studied.

15. A transportable low frequency wave analyser. — H. W. Shipton, Burden Neurological Institute, Bristol.

The automatic low frequency wave analyser described by Baldock and Walter has been re-designed in the light of several years operational experience with the prototype. An attempt has been made to improve the stability, simplify the operating and maintenance procedures, and to produce an easily transportable instrument. This paper will deal with the circuit changes, familiarity with the original circuit being assumed.

A single valve resonant circuit is used, the frequency-determining element being a 3 stage tapered R.C. network. The tapered network has substantially less insertion loss than the original type, uses a minimum of selected or close-tolerance components and occupies less space. The reduced insertion loss permits a conservative design of amplifier, inherently less susceptible to changes in supply voltage and having a wide grid base. The integrator circuits are similar to those used in the original except that a much higher value of cathode resistor is used to obtain improved linearity. Variations in dark current arising from heater voltage changes are minimised by the use of a simple diode compensation circuit.

To avoid the need for a ''floating'' H.T. supply, additional contacts are fitted to the change-over relay so that the stored signals can be applied in the correct sense, to the grid of the write-out valve. This greatly simplifies the power unit, all H.F. supplies being obtained from a single 400 V. 100 m/A. transformer. A ''cascode'' stabiliser is used to feed the resonator and integrator units from a 250 V. line; this has proved superior to gas stabilisers. The 250 V. line is held stable to 0.5 per cent for all acceptable changes of mains voltage; this degree of stability is easily achieved and maintained and is entirely adequate.

The write-out pen is now the cathode load of the output valve which renders unnecessary any capacitative damping and allows the write-out to approximate true ballistic conditions.

The averager is basically unchanged but the use of a ''Dekatron'' cold cathode selector tube has led to a small simple substitute for the earlier P.O. relays, a considerable saving in components and power requirements being thereby effected.

The mechanical details have been painstakingly considered by Mr. W. J. Warren, who is responsible for the construction. An air-spaced continuously rotating switch is used, adapted from the well tried Post Office uniselector. A specially developed 26 way change-over relay allows very long periods of operation (estimated three years normal service) without cleaning or adjustment. Such adjustments as may be required can be made without special tools or unusual mechanical skill. Great stress has been laid on the need for easy access to all operating parts.

The dimensions of the equipment are 24 × 10 × 34 inches high (total volume = 8,160 cu. in.) and

the total weight is 108 lbs. This compares with a volume of approximately 22,000 cu. in. and a weight of 377 lbs. for the currently obtainable commercial version.

In use the equipment has been found extremely reliable and the small space and light weight have enabled the equipment to be carried by car to outlying EEG centres. The analyser can readily be attached to any current British machine and to most American and European equipments. Adjustment of controls has only been required at quarterly intervals and in the course of one year of operation no changes of valves or frequency determining components have been necessary. A commercial version of the instrument could be sold at a price of about £1,200.

16. — A multiple channel cross-correlator for clinical electroencephalography. — E. Geoffrey Walsh, Dept. of Physiology, University of Edinburgh.

Orthodox recording techniques readily yield to the eye data as to amplitude and some information as to frequency. The equally important phase relationships are often more difficult to ascertain requiring detailed examination of the traces, considerable experience and, for all except the slower components, a fast paper drive to obtain adequate resolution. The result of these, and other difficulties (Walsh 1954) is that in practice much clinical electroencephalography depends upon amplitude and frequency alone. Even in published accounts there is commonly no mention of phase relationships. Many clinical studies would be rendered more valuable if these obstacles could be overcome.

Initial studies were directed to ascertaining the extent to which phase reversals were being masked by the interaction of different rhythms. An 8 channel electroencephalograph was used. Four channels were connected to a chain of 5 electrodes in bipolar fashion. The output of these 4 amplifiers was fed through 4 identical resonant filters to be displayed on the other 4 pens. The filters used chokes tuned by parallel condensers. The first instrument used massive chokes of 800 H., each weighed 32 lbs. Later, however, by the use of high permeability cores, chokes of 5,000 H. were obtained that were of small dimensions (Messrs. Amos of Exeter). With paper condensers of up to 10 mfd. satisfactory coverage of even the slower delta waves could be obtained. To avoid damping the resonant circuits were fed through 5 megohm resistors in pushpull fashion and similar connections took the output to the final EEG amplifiers. The Q was 6. At times with this system phase reversals were identified in the tuned channels that could not readily be seen in the orthodox recordings.

It became apparent however that both for these studies and for the investigation of normal records an instrument was needed that would pick out the significant phase relationships automatically. With 4 channels connected in bipolar fashion, 6 paired combinations must be considered. It was desirable therefore that the comparisons should be affected by simple circuitry. For this reason multiplication of the EEG signals (Barlow and Brazier 1954) was not attempted whilst the technique of squaring and adding (Goodwin and Stein 1948) was rejected as an arbitrary procedure. A phase discriminator has been adopted that uses a double diode and few other components. The output depends upon the amplitude of the features common to the two channels when they are compared in phase and in anti-phase. At first each of the 6 similar units fed a microammeter. Deflection of the needle to one side indicated that the signals were in phase, to the other side that the signals were in anti-phase. The results, although interesting, indicated that the full benefits of such a system could only be obtained from a permanent record.

The device was therefore modified and now the output of the 6 units is fed to a motor driven switch and the charge that has accumulated in storage condensers is read every 4 sec. The signals, after amplification, feed an extra pen which thus shows a series of 6 pips in a given epoch. The deflections are upwards when the corresponding channels are in anti-phase, downwards when they are in phase. The size of the pips is weighted according to the size of the signals and also according to the consistency with which phase relationships are maintained. To this extent, the device uses the same criteria as does the electroencephalographer. The system has certain limitations, but it is not unduly complicated and, in practice, appears to be promising.

To facilitate interpretation five of the pips come in a group, one after another, and compare channels 1 and 2, 1 and 3, 2 and 3, 2 and 4, and 3 and 4, in that order. Thus, if the first pip is upwards, there is a phase reversal towards the front of the chain, whilst if the last pip of the series is upwards there is a phase reversal towards the rear. After the sequence of 5 pips there is a gap and the pulse corresponding to channels 1 and 4 stands on its own. Such a comparison is useful when the electrical gradient reverses sign near the centre of the chain, but gathers amplitude towards the ends.

One finding may be mentioned. Channels 1 and 3, and 2 and 4 may be consistently out of phase whilst a comparison of adjacent channels shows little cross-correlation. Such a result would correspond to two current generators — closely placed but independent.

References :

Barlow, J. S. and Brazier, M. A. B. *EEG Clin. Neurophysiol.*, **1954**, *6*: 321.

Goodwin, C. W. and Stein, S. N. *Science*, **1948**, *108*: 507.

Walsh, E. G. *EEG Clin. Neurophysiol.*, **1954**, *6*: 346.

17. An electronic integrator for the automatic measurement of average tension in the EEG.[1] — Zenon Drohocki, Hôpital de la Pitié, Paris.

The electronic integrator permits quantification and coding of the EEG by transforming the signal into terms of the tension integral. This integral (I) recorded automatically and simultaneously with the EEG is expressed in the form of signals whose number (N) in unit time (T) varies proportionately with the envelope of the original signal curve (S). In these conditions the average tension (m) = I/T = S/T = N/T. The apparatus transforms a complex curve into a series of simple signals, thus making the reading and interpretation of the records much simpler and more objective. In order to express the

1 Patented in France by the Centre National de la Recherche Scientifique.

tension integral (I) for a given time (T) it is only necessary to count the number of signals (N) corresponding to this time. To compare the average tensions m 1 and m 2 of two different EEGs it is enough to write down the ratios of the quantities N 1 and N 2 relating to a similar time T, for m 1/ m 2 = N 1/T: N 2/T = N 1/N 2. This comparison is expressed in an unequivocal and quantitative form. When thus qualified the EEG can be subjected to all the procedures required for rigorous scientific analysis.

The results obtained with this measure are independent of the waveform and frequency of the phenomenon concerned; the minimum time for integration is 1/400 sec., the maximum is unlimited. The measurement is made from the beginning to the end of the experiment with no return to zero. The application of this method to research permits, among other things, the quantitative appraisal of changes produced in the EEG by drugs. It is also possible to establish in an entirely objective way the numerical relation between EEG changes and any other physiological variable such as basal metabolism, temperature or blood sugar level. The method is well suited for measurement of the average tension of all electrobiological curves, the quantification of which has so far been fraught with almost insurmountable difficulties.

18. The constant of electrogenesis as a basis for the interpretation of the electrical activity of the brain. — ZENON DROHOCKI, Hôpital de la Pitié, Paris.

The average tension has been chosen as a basis for the quantification of the EEG. The measurements are made with the Electronic Integrator (Drohocki Integrator).[1] Man and animal subjects have been systematically and repeatedly examined in order to work out the norms of quantitative electrogenesis for the brain. The measurements have been carried on continuously for an hour. The most striking fact to emerge in these conditions is the quantitative constancy of electrogenesis as observed over successive periods of a certain duration. The differences between measurements made over successive periods of several seconds are quite large; these differences diminish as the period is increased to the order of tens of seconds and become scarcely perceptible for periods greater than 100 sec., disappearing altogether for periods of 200 to 300 sec. Thus, when devised for a long enough period of observation the average tension reaches a steady level characteristic of each subject examined.

This *constant of electrogenesis* can be studied with the full rigour of statistical analysis; in fact the statistical distribution of the measures for very long periods is always a normal one, characterised by a low variance as well as by an astonishing personal stability of the mode and the mean. The constant of electrogenesis, defined quite precisely, does seem to be a trustworthy and objective reflection of the electrical changes in the brain. Any modification of cerebral activity should be compared with the constant of electrogenesis and this comparison expressed in significant figures. In fact, basic alterations in the electrical activity of the brain are associated (according to whether it is a matter of increase or decrease) with a displacement of the mode to the right or the left of the distribution curve. At the same time there can be seen significant changes in the mean. Thus any valid changes in electrogenesis produced by physiological, pharmacological, or pathological agencies can be expressed in precise figures.

This constant of electrogenesis, centred around an individually characteristic value, implies the existence of a regulating mechanism similar to those which deal with other physiological phenomena such as temperature, basal metabolism, blood Ph, blood sugar, and the like. For example, it is possible to demonstrate quantitative changes in electrogenesis as a result of excitation, inhibition, hyperpnoea and sleep.

19. A standard quantitative method for use in cerebral pharmacodynamics. — ZENON DROHOCKI, Hôpital de la Pitié, Paris.

Quantification of the EEG by means of the Electronic Integrator (Drohocki Integrator) has permitted the development of a standard method of studying the pharmacodynamics of the brain.

The principle of the method, which is applied without variation to any substance which acts at the level of the brain, is as follows: some hours before the experiment, under a local anaesthetic, electrodes are screwed into the skull without piercing the inner table. In this way the duration of the experiment can be prolonged almost indefinitely. Then, with the animal wake, free to move and without any restraint by the apparatus, the EEG and the integral are recorded for half an hour. The constant of electrogenesis in the wakeful stage can then serve as a reference. The latter is worked out from the statistical distribution curve and its usual parameters: mean, median, variance and error. These data are derived from 1,800 measurements corresponding to the 1,800 sec. of recording. After administration of the compound to be studied, the recording is continued without a break to the end of the experiment. The average tensions are extracted for convenient consecutive periods chosen to be between 10 and 60 sec., and these are then compared with the reference value. This comparison is made by means of suitable statistical procedures, particularly by the t-test of Fisher which allows comparison of a large population (N = 1,800) with a small sample (N = 60). Since the numerical data for the calculations that have to be made are the same for the whole experiment — the only change being to the value of the integral — the final formulae are very simple.

This procedure therefore has the double advantage of speed and accuracy. It is possible to work out with great rigour the quantitative variations in electrogenesis characteristic of the drugs under investigation. In fact this procedure permits definition at every moment and in figures of:

1. The total amount of electrogenesis.

2. The sense of any change (increase, decrease, stable).

3. The slope, that is, the rate of change between the points of measurement.

4. The duration of any state.

To demonstrate these features there will be described the effects of: Cardiazol, amphetamine, curare, urethane and Nembutal.

---

1 Patented in France by the Centre National de la Recherche Scientifique.

20. Personal remisiscences of Hans Berger. — Rudolf Lemke, Department of Psychiatry and Neurology, Friedrich Schiller University, Jena.

Berger, for a long time physician superintendent and later successor to Binswanger, was Professor of Neurology and Psychiatry in Jena from 1919 to 1938. In 1925, for the first time, he succeeded in obtaining brain potentials from man, but only in 1929, he writes, "after five years of silent work, disturbed by the many difficulties besetting a clinician, have I published my discovery". (Hans Berger: Das Elektroenkephalogramm des Menschen. Halle, **1938.**)

When I joined the Neurological Clinic as an assistant in 1931 probably no-one sensed Berger's greatness nor the significance his name would assume in our discipline. In his day he had a reputation as an outstanding clinician and, especially, he was a fine judge of cerebral localisation of brain disorders. Amongst his fellows his work on physiology, the circulation, and the temperature of the brain was known, but few only knew of his electrical investigations in the early days. Berger himself never talked about it without being asked: during the several semesters I had been his lecture assistant I never knew him to speak during his course on his own field of research.

Only in 1931 did I hear him give a paper at a meeting of the Medical Society at Jena on his discovery, the EEG. I can well remember that the interest amongst his colleagues who listened to him was not very great. From the specialists in internal medicine there came on this occasion the objection that the electrical oscillations demonstrated were currents not from the brain, but from muscle. Subsequently, Berger occupied himself with this question and by means of a correction — as he himself wrote — he amended his error.

From the year 1933 onwards, I was permitted to help Berger with his electrical brain investigations by taking photographs of the traces. The apparatus was not easily worked; we used an oscillograph by Siemens, a highly sensitive instrument, usually connected to a coil galvanometer, for our representation of the EEG. The traces were recorded by photography. In a darkened room next door, on a comfortable examination couch, lay the patient and Berger made his observations, communicating with us by visual signals about the commencement of his tests, about absences and the like. His method of investigation, compared with present day ones, was rather primitive. We were happy if we obtained as much as 3ft. of useful graph from a patient in those days and often enough the experiment failed. It must arouse our admiration that Berger, with such simple equipment, found all the basic patterns of the EEG, recognised them, and interpreted them correctly.

The lectures which Berger gave each year on his researches to the Medical Society of Jena found no greater appreciation as time went on, and he often became discouraged; in 1934, at the meeting of German Neurologists and Psychiatrists he reported on the EEG, at Munster, and there too he did not arouse the interest he had expected.

Berger was all the happier with the agreement and interest abroad; Adrian and Matthews at Cambridge, Grey Walter in London, and Davis, Gibbs, Harvey and Dusser de Barenne in the United States wrote appreciative letters and took an active interest in his work. Some of these visited us before the war.

In 1937 Berger had the honour of receiving invitations to read papers to the International Psychological Congress in Paris and in Bologna on the occasion of the Galvani Memorial Celebrations; the papers occupied his mind much and the notes for them are still in our archives. Shortly before the beginning of the war he was invited to give a series of lectures in the U.S.A. Twice Berger had been proposed for the Nobel Prize; once immediately before the war, when the Hitler regime prevented him from accepting this honour, and again after the war there came an enquiry, but Berger had died.

Berger was no adherent of Hitler and so, at the age of sixty-five, he had to relinquish the service of his University; not having expected this, he was gravely hurt, all the more as he had great plans for work. For him, a trying time had begun. He had predicted the impending troubled events to me in private conversation before the war.

The loss of his place of work, the lack of any possibility of continuing his EEG researches (at this time he instructed me to take up his work once again) and the events of the day, bestowed upon him a depression which finally killed him. I was able to obtain a death mask.

21. The EEG during hypothermia in paralysed cats. (Cortical and subcortical changes, electrical responses to auditory stimuli and convulsive discharges). — M. Jouvet, O. Benoit, J. Courjon and M. Tanche, Neurophysiological Section, Laboratory of Physiology, Lyon.

1. Experiments were performed on kittens paralysed with Flaxedil and artificially ventilated. Cortical and subcortical activity was recorded with an EEG machine. Lowering of the body temperature was procured by an ice bag. The temperature of the body was measured with a rectal thermometer. It was possible to obtain temperatures under 10°C.

2. The electrocortical and subcortical activity during cooling can be classified in three phases:

(*a*) From the normal temperature to about 25°C, alternation of normal high voltage fast activity, and spindles at 10 c/sec.

(*b*) From 25°C to about 15°C, paroxysmal activity at 14-16 c/sec., alternating with high voltage slow spindles at 5 c/sec.

(*c*) From 15°C to 8°C, low voltage slow activity.

3. Electrical responses to auditory stimuli show an increase and spatial spread of cortical responses with spike and wave patterns and slow afterdischarges. These are quite a secondary response.

Auditory responses disappeared at 22°C in the specific auditory pathways, earlier in the non-specific pathways (reticular formation).

4. Constantly, at about 17°C spontaneous spike-and-wave patterns appeared, synchronously and bilaterally. Epileptic seizures occurred then.

5. The significance of these findings, particularly the role of epinephrine and homeostatic mechanisms are briefly discussed.

22. The action of Reserpine on the EEG of the rabbit. — P. Gonnard, H. Schmitt and S. Nechtschein, Laboratoire d'EEG, Maison Départementale de Nanterre, Seine.

Reserpine, unlike barbiturates, and in spite of its sedative action (Bein 1953) does not antagonise the action of convulsants but, on the contrary, seems to assist it. The effect of this compound on the elec-

trical activity of the cortex has been studied in various ways. According to Monroe and his collaborators it produces in man a record like that of natural sleep. Rinaldi and Himwich find that in curarised animals, the magnitude of the blocking responses is increased; there would thus seem to be a discrepancy between the EEG and the tranquillising effect on behaviour.

Longo and Napolitano obtained a diphasic action in the curarised rabbit; first, 20 to 30 min. after injection of the alkaloid there was desynchronisation of the EEG and prolongation of the blocking reactions, then, one or two hours after the injection, slow waves appeared, while the blocking reaction was suppressed.

These contradictory results suggested that it would be worth studying wakeful and uncurarised rabbits so as to be able to compare the behaviour of the animals with the EEG. After making 4 holes and fixing electrodes in them under ether, the rabbits were left to come round. The experiment was begun one hour after; the animal was put into a special box with a hole for the head to protrude from, so that the movements were restrained as much as possible without upsetting the results too greatly.

We have confirmed the existence of the two phases described by Longo and Napolitano. In the first place the spontaneous record is activated and there is protraction of the blocking reactions induced by sensory and chemical stimuli; one hour after the injection large slow waves appear. At the same time the blocking reactions are diminished and abbreviated. During the activation phase the animal stays awake; however, the motor responses to stimuli are reduced in spite of the intensity of the blocking reactions. With the appearance of the slow waves clinical sedation becomes quite obvious; the animal is ataxic, lies on its side and goes into a state of easily reversible torpor.

If amphetamine is exhibited during the sedation phase, it acts as a powerful antagonist to Reserpine, awakening the animal and desynchronising the record.

Reserpine does not abolish the clinical and electrical seizures produced by Metrazol, but it does control convulsions due to caffeine. None the less, caffeine in convulsant doses does desynchronise the record.

Reserpine would seem to be a drug which acts on the ascending activating system of the brain stem, which it first excites and then inhibits. In this it differs from chlorpromazine since the sedative action is only a secondary one.

The drug is comparable with barbiturates and other general anaesthetics in its diphasic action; it is distinct from them in the extent of the activation phase and by the fact that it does not induce deep sleep, nor marked inhibition of the action of excitatory drugs on the nervous system.

23. The electroencephalogram of circumscribed cerebral lesions under Pentothal sensitisation and pharmacodynamic cortico-subcortical exploration. — J. Schneider and D. G. Thomalske, Laboratoire d'EEG, Hôpital Pasteur, Colmar.

The aim of this paper is:

1. To describe certain of the Pentothal induced neurophysiological mechanisms which give rise to:
   (*a*) The electrographic fast activities stage (anesthetic induction stage),
   (*b*) To the stage of the K-complex and secondary discharge.

2. To put into evidence the disturbances of these electrographic stages which may occur under the influence of various cerebral diseases — especially neoplastic affections — the cortical or sub-cortical localization being determined by operation, autopsy or by the usual neurosurgical techniques.

3. To analyse, based upon these electro-clinical data in man, the neuronal systems used:
   (*a*) By the ascending reticular impulses which evoke the fast electrographic activities.
   (*b*) By the corticipetal impulses which elicit the K-complex.

4. To illustrate, with these data, the part played by a pharmacodynamic exploration for a more precise localization of a delimited cortical or subcortical lesion.

24. The electroencephalogram in barbiturate addiction during withdrawal. — M. Hertel Wulff, St. Hans Hospital, Copenhagen.

Electroencephalograms were obtained from 87 patients during 96 admissions to psychiatric division of the University hospital because of barbiturate addiction. Medication was withheld during hospitalization. The findings during withdrawal — the electroencephalograms, barbiturate blood levels and clinical status are presented.

The electroencephalograms were obtained within the first few days of admission and repeated once or twice a week until they had returned to normal or showed no further change. Eight scalp electrodes were used and both scalp-to-ear and scalp-to-scalp recordings obtained on a Kaiser 6-channel electroencephalograph. The 30 min. recording included 3 min. of hyperventilation and 5 min. of photic stimulation (Alvar stroboscope) with eyes closed and open at rates between 2 and 50 per sec. Blood barbiturates were determined by means of their specific ultraviolet absorption spectra. (Lous, P. *Acta pharmacol. toxicol,* **1950,** *6*: 227).

The patient material consisted of 29 men and 58 women two thirds between 30 and 50 years of age. The barbiturates taken were short acting (56 patients), long acting (11 patients) and mixed or unknown (29 patients). The fall in blood barbiturate of the short acting drugs (aprobarbital, amobarbital) was 25-60 per cent and for the long acting drugs (barbital, phenobarbital) 12-27 per cent per 24 hour period. The initial blood barbiturate concentration average 5 mg. per cent (3-10 mg. per cent).

Severe Withdrawal Symptoms (convulsions and psychosis) appeared only in patients addicted to short acting and mixed barbiturates. Of the 85 patients in this group 13 developed convulsions, 5 psychosis and 16 both convulsions and psychosis. These symptoms developed at a time when the barbiturate blood level had fallen to 0-1 mg. per cent, usually on the fourth to sixth day after withdrawal. The convulsions were usually single and were not treated with medication. The psychosis lasted on the average 4-6 days (in one case 3 weeks) when not treated.

A family history of epilepsy was obtained in 12 per cent of 43 patients without withdrawal convulsions and in 20 per cent of 29 patients with withdrawal convulsions. In the latter group only two had a history suggestive of epilepsy although an additional 17 had had convulsive episodes most probably in relation to barbiturate withdrawal. Of the patients without withdrawal convulsions two had a history of epilepsy.

The first EEG taken when the blood barbiturate level was high, was abnormal in 24 of 42 patients; 13 showed fast and 9 slow activity in the resting record; this distribution was the same in long and short acting barbiturate addiction. Paroxysmal abnormalities appeared only in patients addicted to short acting or mixed barbiturates (with the exception of two epileptic patients: in two patients in the resting record and in a fifth of the patients during photic stimulation.

The maximal incidence of paroxysmal abnormalities was on the fourth to sixth day after withdrawal: in 17 per cent of 85 patients in the resting record and in 62 per cent of 81 patients during photic stimulation. The paroxysmal abnormalities lasted usually two weeks (8 weeks at the most).

As to clinical and electroencephalographic correlation, of 29 patients with withdrawal convulsions, 23 had paroxysmal EEG abnormalities. Of 56 patients without withdrawal convulsions, 30 had paroxysmal abnormalities.

It seems probable that it is the rapidity of excretion rather than the type of medication which is responsible for the incidence of clinical and EEG withdrawal phenomena.

This view is supported by the findings in a patient with bromide intoxication whose blood bromide level was brought from 236 mg. per cent to 36 mg. per cent in the course of two hours through an artificial kidney. She developed paroxysmal EEG changes on photic stimulation, otherwise unusual during bromide withdrawal.

That even small doses of amobarbital can produce paroxysmal EEG changes on withdrawal is indicated by seven non-addicted patients who received 0.8 g. daily for two weeks. Three of these had paroxysmal changes on photic stimulation in the withdrawal period.

In summary, electroencephalographic abnormalities were more common than clinical symptoms in the period of withdrawal in barbiturate addiction. The abnormalities were most frequent on the fourth to sixth day after withdrawal and manifested themselves as paroxysmal abnormalities during photic stimulation (62 per cent). Both clinical symptoms and EEG abnormalities appeared almost exclusively in patients addicted to short acting barbiturates.

25. Comparative effects of Metrazol and Megimide in activation of epileptic patients. — JEAN COURJON and HÉLÈNE BONNET, EEG Laboratory, Edouard Herriot Hospital, Lyon.

The recent paper of Delay *et al.* at the French Society of Neurology stimulated us to compare the action of these drugs on the same patient.

Each patient received one injection of Metrazol according to Gastaut's technique (50 mg. every 30 sec.), and the next day an injection of Megimide under the same conditions, first one cc. per 10 kg., then one cc. every 15 sec. A short photic stimulation was performed 3 sec. after the injection of each.

The effects of megimide are very often comparable to those of Metrazol: there is the same type of abnormality and the same topographical distribution.

Megimide is not always as efficient as Metrazol: in three cases no effect was observed.

Less often abnormalities with Megimide are more localised, producing a better "activation".

No seizure was induced by Megimide; Metrazol activation produced two clinical fits.

Megimide was always well tolerated; very frequently unpleasant vegetative side-effects were observed after Metrazol.

This new activation method seems to us very interesting. This study is to be continued.

26. Comparison of EEG "activation" by pentamethylenetetrazol (Metrazol) and Bemegride (Megimide). — G. DROSSOPOULO, H. GASTAUT, G. and J. VERDEAUX and E. SCHULLER, Faculté de Médecine, Marseille.

Bemegride was suggested as an EEG activator by Delay, Schuller, Drossopoulo, Haim, G. and J. Verdeaux in February 1956. Assuming that its mode of action differs little from that of Metrazol and in order to compare the two, it was decided to follow up the study of the drug in the central EEG Laboratory of the Marseille Hospitals which have specialised in Metrazol activation.

Three groups of patients have been activated; one by Bemegride, one by Metrazol, a third by both compounds. Most of these patients were epileptics, but other neurological and psychiatric patients were included. All the records were then compared and the following conclusions were drawn:

1. Bemegride modifies the EEG in the same sense as Metrazol.

A. The drug evokes in all subjects, normal or abnormal, changes of two types,

(i) Progressive modifications in the form of slow bilateral synchronous activity.

(ii) Paroxysmal modifications in the form of bi-synchronous multiple spikes and waves, either spontaneous or provoked by flicker, liable to end in the development of a generalised epileptic discharge.

B. In subjects with cerebral disorder it causes the appearance of changes which are never seen in normal subjects:

(i) Bisynchronous discharges of rhythmic 3 c/sec. spikes and waves.

(ii) Focal discharges of spikes, slow waves, or spikes and waves: sporadic discharges, unaccompanied by clinical symptoms (interseizure discharges) or rhythmic discharges accompanied by partial epileptic seizures (seizure discharges).

2. Bemegride injected intravenously in 0.5 per cent solution changes the EEG much more slowly and progressively than Metrazol in the same concentration. As a general rule rather more than twice as much Bemegride, injected in the same time, must be used to obtain equivalent effects.

3. Activation by Bemegride is easier for the patient to bear than by Metrazol, for it has few disagreeable subjective side-effects during the test and after it, even when a seizure has been provoked. It is more useful for the physician, since the EEG changes produced are less abrupt and the partial seizures that may be set off are less liable to become generalised. From the clinical standpoint, the seizures evoked by Bemegride, like those due to Metrazol, closely resemble the spontaneous ones in any particular patient, but the resemblance is even closer than with Metrazol which often tends to truncate the onset of the attack, particularly the subjective features.

4. There is some reason, therefore, for replacing Metrazol with Bemegride as an EEG activator; all the more because the compound is physiological, is quickly excreted and can be neutralised almost immediately by an injection of barbiturate. Of course, the method of activation is at the discretion of the physician who may study, according to his principles, or the requirements of his investigation:

(i) Either the first progressive non-specific abnormalities (threshold studies as described by Ziskind and Bercel).
(ii) Or, the first non-specific paroxysmal abnormalities, either spontaneous or evoked by flicker (threshold test), the photomyoclonic effect as elaborated by Rémond and Gastaut,
(iii) Or again the specific inter-seizure abnormalities (focus study).
(iv) Or lastly the specific seizure abnormalities (seizure study, to compare the clinical and EEG manifestations).

27. The effects on the EEG of Centropneine. — D. Santenoise and C. Szalewska, Centre de Biologie Thermo-Climatique, Paris.

Lengthy research has resulted in the isolation of a pancreatic hormone which has the specific effect of regulating the respiratory centres; this has been given the name Centropneine.

Administration of this hormone in man, dog, guinea pig and rabbit is followed by an increase in the sensitivity of the respiratory centres to CO_2 and a lowering of the CO_2 level of the blood.

In subjects with damaged respiratory centres the respiratory deficit is increased following administration of Centropneine.

A. Since the administration of this hormone to asthmatics for a long enough period is followed by relief, spacing out and even disappearance of the attacks, it was thought worth while to study the action of Centropneine on the abnormal EEG records shown by some asthmatics.

In 14 asthmatics the following facts were observed:

1. In asthmatics with a normal EEG, the record is not affected by Centropneine.
2. In asthmatics with an abnormal EEG, mostly of the dysrhythmic type, the record becomes much more stable after injection of Centropneine, alpha waves have been found to appear.

B. We wondered whether the powerful ventilating action provoked by the injection of Centropneine might not involve, as in the hyperpnoea test, the appearance of pathological patterns in some subjects.

We have thus been able to show a close parallelism between the reaction to hyperpnoea and those to Centropneine.

28. The use of chlorpromazine as an activating agent. — Galatea Lyberi and S. L. Last, EEG Department, London Hospital, London.

Our interest in the use of chlorpromazine as an activator was aroused by a chance observation. When examining patients with sphenoidal electrodes, chlorpromazine was given on a few occasions to keep the patient quiet. It seemed to us as if this were particularly effective in increasing abnormality, which had been present to a lesser degree, or not at all, in the resting record.

This study deals with a small number of cases — 27 —whose ages vary from 8 to 50: 2 of these cases were patients in whom a tumour was found, one a glioma and the other a meningioma. In 7 cases the existence of atrophy or a porencephalic cyst was established by biopsy or air encephalogram. Seven other cases had either clinical evidence or cortigraphic evidence of the temporal lobe type of epilepsy. In 13 cases a comparison with Seconal was made. In most of them the activating effect was as good, or better, than that of Seconal and in only one or two was the effect rather less than with Seconal.

Chlorpromazine was given intravenously. The usual dose for an adult was 25 mgm. and for children 15 mgm. The following effects could be seen:

1. In some cases sharp waves or spikes appeared under the influence of chlorpromazine, where they had not been present in the resting record. There were other cases where sharp waves had been present before and where chlorpromazine made them sharper, i.e. lessened their duration.

2. Three effects of the theta activity were seen:
(i) The frequency was sometimes lowered, the activity becoming slower than it had been in the control record;
(ii) the voltage was sometimes increased, and
(iii) it was noticed that in some cases the theta activity became more localised.

3. Beta activity did not appear in the generalised way in which it does following Seconal or other barbiturates, but appeared one-sided and occurred on the side of the lesion; in other words, it was a positive localising sign, not a negative sign as it often is with Seconal, where its absence is often noted on the affected side. It sometimes occurred in a comparatively small area, and in one case it was later confirmed by an electrocorticogram that a corresponding area of the cortex was atrophic and showed beta activity.

4. A more curious effect consists of the appearance of rhythmic 14 c/sec. activity. It occurs in short runs and is of low voltage. The frequency makes one think of the spindles occurring in spontaneous or induced sleep but the activity described above does not show the waxing and waning that gives the spindles their characteristic appearance. They start rather suddenly and finish equally suddenly.

5. In one case interesting complexes appeared, which had not been present in the resting record. These consisted of groups of spikes, followed by one slow wave component. These complexes were well localised in an area where later cortical atrophy was confirmed by air study.

An interesting feature of the chlorpromazine effect is that it takes some time to establish itself. As a rule the maximum effect occurs after 45 min. to an hour but sometimes it had already started after 25 min., and the effect was often prolonged — sometimes it lasted up to 2 hours.

In this study we have confined ourselves to cases where a localised lesion was suspected and in this we differ from Turner, Berard, Turner and Franco.

We have found that in our material 19 out of the 27 cases gave a useful result: by useful we mean that it either showed local abnormality which was not present before or enhanced an abnormality which could be seen less distinctly in the resting record.

It will be interesting to speculate on the mode of action of chlorpromazine but little can be said about it, except that it is almost certain to be a central effect. There is some evidence that chlorpromazine acts on subcortical structures, possibly on the reticular formation, which at the moment seems to be blamed

for most electroencephalographic findings. A good deal of further research will have to be done before any such assumption can be regarded as proved.

To sum up, it seems to us justified to use chlorpromazine in trying to establish local abnormality.

29. The effect of intravenous chlorpromazine on the EEG of epileptic patients. — W. Fabisch, Mapperley Hospital, Nottingham.

This investigation was started because seizures were reported in the literature to occur after chlorpromazine in epileptics previously stabilized with anticonvulsants and free from fits.

Material and Methods

(*a*) Epileptic patients whose EEG characteristics were known (with the sole exception of one child) were selected from both a mental hospital and an out-patient clinic. They were grouped as follows:

1. Those with grossly abnormal records (20 cases).
2. Those with fairly normal inter-seizure records (20 cases).

Members of the two groups were as far as possible paired for the trial.

(*b*) A control group of patients from the hospital excluding any cases with fits, head-injuries, brain surgery, recent administration of ''tranquillizing'' drugs, and electric convulsive treatment for at least 4 months. This group included 20 patients with the following diagnoses: psychoneurotics, unstable personalities, early young schizophrenics and middle aged paraphrenics.

(*c*) A solution of 25 mg. chlorpromazine in 10 cc. of saline was prepared and injected intravenously at a rate of 2.5 mg. per 1-1½ min. up to a maximum of 0.3-0.5 mg. per kg. body-weight. Control EEG's, including overbreathing and photic stimulation were taken, after which the drug was injected and the EEG continued over the following 35-40 min.

Results

Controls: After about 15 min. there is a general decrease in amplitude accompanied by drowsiness. Frequencies decrease, first over the posterior parts (e.g. alpha activity drops from 10-11 c/sec. to 8-9 c/sec.) 5-7 c/sec. activity becomes more prominent and spreads from the posterior parts to the intermastoid plane and sometimes further forward. Three-4 c/sec. lambda waves appear. After 20-30 min. there is further flattening of the EEG. On spontaneous stirring, after noises, touching of the skin, turning on the light in the room, faster activity of higher amplitude returns for a few seconds or there are more typical K-complexes. At the end of the recording, the patient usually falls asleep for about half an hour.

Epileptics with fairly regular inter-seizure recordings: In all except one the picture was essentially the same as described above. One patient showed bilateral posterior temporo-parietal low amplitude sharp waves (or spikes) in runs lasting several minutes.

Epileptics with usually abnormal recordings: In 2 patients no abnormal features were seen after injection. One had shown a short classical petit mal burst during overbreathing, the other right sided parietal spikes for about 3 sec. also during overbreathing. In the remaining 18, the following changes were observed:

(*a*) The abnormal features occurred for more prolonged periods.

(*b*) The abnormal features occurred more frequently.

(*c*) The abnormal wave forms increased in amplitude against a flatter background.

(*d*) Asymmetries became more conspicuous.

(*e*) Acoustic and tactile stimuli caused in some cases an increase of the abnormal activity, apparently related to changes in the depth of sleep. As a rule several of these changes were seen in one single case.

Discussion :

The findings show that intravenous chlorpromazine in doses of 0.3-0.5 mg. per kg. body weight can cause increased paroxysmal cerebral activity in unstable interseizure EEG's of epileptics. No convulsive seizures were observed in this series. However, in some of the patients with generalized abnormalities (petit mal pattern and multiple spike and slow wave discharges) changes in the rhythm of breathing and apparently involuntary opening of the eyes suggested alterations of consciousness. The findings make it probable that, with higher and more sustained doses of chlorpromazine combined with reduction of the usual anti-convulsant when reliance is placed on the ''tranquillizing'' effect of chlorpromazine, convulsive seizures should occur more frequently.

30. Behaviour and EEG changes in "Parkinsonian" states induced by prolonged treatment with chlorpromazine and Reserpine. — F. Flugel, D. Bente and T. Itil, Universitats-Nervenklinik Erlangen, Germany.

By prolonged treatment with a combination of chlorpromazine and Reserpine, we were able to induce a ''Parkinsonian'' state in psychotic patients. This has proved to be a very effective therapy in otherwise resistent cases, more so than the usual therapeutic methods. For this reason, we have applied it systematically to a large group of psychotic patients; 115 cases have been statistically analysed to date. In 77 per cent of these cases, a pronounced ''Parkinsonian'' state could be noted; in 19 per cent, the syndrome was less well-defined. In only 4 per cent no significant reaction was observed.

This state (akinetic-aboulic syndrome), which is usually preceded by a shorter or longer transition period of restlessness, is characterised by behavioural changes ranging from decreased spontaneous activity over states of extreme passivity to catalepsy. There is a shift in the balance of autonomic functions, and the cyclical alternation of sleep and wakefulness is disturbed. Although all reactions are excessively slow, we observe no dissolution of intellectual functions (behaviour, performance tests).

In connection with these modifications of behaviour, we find marked electroencephalographic changes. These are produced by the synergic interaction of the effects of chlorpromazine and Reserpine. As we have described elsewhere more extensively, long term medication of chlorpromazine leads to synchronisation, regularisation and stabilisation of electrical activity. Prolonged high dosage treatment with Reserpine, however, has considerable slowing effects (especially over the fronto-central areas) and may even produce slow delta activity. The combinations of both medicaments results in characteristic patterns of steady synchronous slow activity. Blocking reactions to psychosensory stimulation are frequently attentuated or abolished. The extent to which these changes in the EEG occur depends on

the basic electrical activity which was characteristic for each patient before the beginning of treatment. Especially EEG's with rapid background activity and a tendency to desynchronisation show a relatively high resistance towards the drug-induced alterations.

The EEG findings described above seem to indicate a considerable lowering of the level of central activity which might result from a decrease of the activating impulses transmitted by the diffuse non-specific projection system.

The clinical syndrome, i.e. inhibition of psychomotor activity, decrease of vigilance and diminished reactivity to external and internal stimuli, can also be seen in accordance with such an interpretation. The mechanism involved here seems to be a fundamental factor in the therapy of ''endogenous'' psychoses.

References :

D. Bente and T. Itil. *Arzneimittelforschung,* **1954**, S. 418-423.

D. Bente and T. Itil. *Med. Klinik,* **1955**, S. 1296-1301.

D. Bente. Colloque international sur la Chlorpromazine et les médicaments Neuroleptiques en thérapeutique psychiatrique, Paris, *Encéphale* (in press) Oct. 1955.

F. Flügel, *Verhandl. Dtsch. Ges. inn. Med.,* **1954**, 60.

F. Flügel. *Medizinische Klinik,* **1955**, S. 509-510.

F. Flügel. *Medizinische Klinik,* **1955**, S. 634-635.

31. An alpha correlate to behaviour changes produced in psychotics by intraventricular injections. — J. P. Farrell and S. L. Sherwood, Severalls Hospital, Colchester, Essex.

Some effects on the EEG of psychotics treated by intraventricular injections of cholinesterase (ChE), Serotonin, banthine and some other drugs, detectable by routine examination of the records, have been reported elsewhere (*Proc. Roy. Soc. Med.*, **1955**, *48*: 855-863) 30 patients have been treated by this method to date, the majority being schizophrenics with catatonic features. Before this treatment their records were either arhythmic and of low voltage, or they showed a variety of rhythms within the beta, theta and alpha bands and, some, also repetitive complexes. The present paper deals only with the changes of alpha characteristics, for the patients' mental state appeared more closely related to these than to other features of the EEG.

The records of 7 cases recently observed and treated were examined by a method intended to provide a measure of the changes in the alpha band without the use of an analyser which we still lack. Amplitude, frequency and distribution were each known to change with the mental state. It was therefore thought desirable to use ''performance'' in a given place as an appropriate function of the data obtained. In any one of the 7 to over 50 records obtained from each of the 7 patients, 3 derivations — longitudinal and transverse occipital, and transverse temporal — were analysed in the following way: an upper and lower tangent were applied to the highest alpha waves of a sequence of 10 successive waves, the sequence of highest amplitude having been chosen from a run of not less than 5 min. The distance A between the levels of the midpoints of the 2 tangents is measured and divided by the length of the ten-wave sequence and multiplied by the frequency. Thus $P = \frac{A}{10\lambda} \times F$ was taken as the expression of the best performance in a given run. The behaviour was assessed clinically taking into account the patients reactivity and the relevance of the reactions. This was charted in 5 arbitrary units, 1 denoting catatonic stupor and 5 approach to normal even if such reactions were simple and childish. The data so obtained were plotted for each case over the varying periods of weeks, months and years, with and without treatment.

The results are as follows:

ChE : There was a rise alpha *performance* in the occipital regions in all cases with a single exception (this patient was not a schizophrenic, and had a leucotomy 8 years earlier), and there is no such rise or a fall in the temporal regions; these changes are commensurate with the mental changes. Alpha *frequency* dropped in all cases except one or changed in such a way that the figures were close to one another; never was there a rise in the figures of the temporal regions, and the improvement was related to the congruity of the frequencies measured.

Serotonin : There was usually a rise in performance (following a transient fall immediately after injection) and also in frequency, including the temporal and occipito-temporal regions. Behaviour was characterised by a marked increase of reactivity but not of relevance; small and widely spaced doses have a more beneficial effect than larger or frequent doses.

Banthine : Only 2 cases in this group have been analysed: where there was a rise of performance in the longitudinal occipital traces only and a fall in the others, behaviour improvement was greater than in the case where the transverse occipital attained the highest performance. This latter case showed a fall, the former a rise in frequency of the occipital and a fall in the temporal regions.

In conclusion, the degree of improvement of a patients behaviour, with intraventricular injections, is reflected or preceded by changes in the alpha rhythm with respect to (1) frequency, which should uniform, and certainly not higher in the temporal regions than elsewhere, for mental well-being; this associated also with (2) performance which should be higher in the occipital than in the temporal regions.

As yet it is impossible to predict with certainty which drug would suit a given patient best, but there is no doubt that the beneficial effects of ChE are greater than those of banthine, and that Serotonin in small doses may somewhat improve but in large or continued doses aggravate behaviour. It is hoped that with instrumental analysis more, and more precise information will be obtained. It is important to realize that we are dealing with phenomena in time and timing, so that changes are of greater importance than states.

32. The EEG as a means of appraisal of new anticonvulsant drugs with particular reference to acetazolamide (Diamox). — R. A. H. Morison, W. Grey Walter, A. L. Winter, Burden Neurological Institute, Bristol.

The lack of resources for large scale statistical studies of new anti-epileptic drugs makes it desirable that small scale investigations be carried out with as much accuracy and detail as possible. This paper

deals briefly with one such pilot experiment, carried out early in 1956, where the evaluation of Acetazolamide in the control of petit mal cases was undertaken at the Burden Neurological Institute.

A method of evaluation of drugs for the control of major epilepsy is being worked out, but will undoubtedly raise fresh difficulties as certain hazards are present which did not concern us in the current survey. For example, in dealing with minor epilepsy it is possible to stop all the patient's medication for a few days and exhibit a new drug from zero. This could not be done with major epileptics without running the serious risk of precipitating *status epilepticus*.

The method used entailed careful selection of suitable cases from a large outpatient clinic at the B.N.I. The cases chosen were required to meet the following criteria:

1. They must show clearly defined clinical evidence of petit mal — objective signs such as head-shaking or obvious fixation of posture during each minor attack.

2. The attacks must be associated with a well marked classical wave-and-spike pattern on the EEG.

3. The patients should be subjectively aware of their attacks so that they can keep a record of the number per day.

4. They should not have many major attacks.

Out of several minor epileptics admitted for research purposes, 3 were found to meet the above criteria and were chosen for a 4 week detailed study. The co-operation of the patients was encouraged throughout the experiment. This was found to be of considerable value in assessing certain phenomena such as side effects, the patients being quite unaware that placebo control tablets were used on occasions.

Regular EEG recordings were made throughout the test period, covering each change of drugs. These were combined with objective clinical data and subjective findings as noted by the patient in a diary, where note was also made of the number of minor attacks and any emotional disturbance.

In general, the profusion of seizure patterns in the EEG followed closely the clinical and subjective report of seizure incidence. In subject (R) there was a dramatic disappearance of seizure patterns two hours after the exhibition of acetazolamide. The interseizure records were less clearly correlated with clinical and subjective data. In case (P) the records became "normal" during combined administration of acetazolamide and phenobarbitone. In case (K), where the interseizure records were more grossly abnormal, the basic pattern remained abnormal even during periods of marked clinical improvement.

The EEG observations suggest firstly, an adjuvant relation between acetazolamide and other anticonvulsants and secondly, the existence of adaptive or differentiating mechanisms such that the adjuvant properties of acetazolamide tend to wear off in the course of days or weeks (R): the efficacy can sometimes be restored by withdrawal and subsequent re-administration of the drug.

(The Authors gratefully acknowledge permission granted by Professor Golla to select the cases from his extensive epileptic clinic. Our thanks are due to Lederle Laboratories for generous supplies of acetazolamide (Diamox).

33. Mephenesin and myoclonic epilepsy. — J. H. D. Millar, Royal Victoria Hospital, Belfast.

Eight patients suffering from progressive myoclonic epilepsy were described recently (Harriman and Millar, *Brain*, **1955**, *78*: 325). Three brothers were treated with Mephenesin as described by Kelly and Laurence, (*B.M.J.*, **1955**, *1*: 456). One has improved considerably and the effect on the EEG of a 1 per cent solution was dramatic. The myoclonus probably originates from a discharging centre in the brain stem (Haguenan *et al.*, 1950 and Gastaut *et al.*, 1951 and 1952) and this view is supported by the fact that the main pathology is situated in the brain stem. Mephenesin has been reported to reduce the wave and spike activity in petit mal epilepsy (Gammon and Churchill 1949). There is suggestive evidence therefore that Mephenesin has an action at the level of the brain stem.

34. Caffeine sodium benzoate, its effect on the slow activity associated with supratentorial tumours. — J. H. D. Millar, Royal Victoria Hospital, Belfast.

Caffeine sodium benzoate 7½ gr. intramuscularly at 6 hourly intervals has reduced the slow activity in the EEG associated with supratentorial tumours in some patients. Shenkin (1950) measured the effect of caffeine sodium benzoate on the cerebral blood flow by the nitrous oxide method. He found a significant reduction in cerebral blood flow 5 min. following the intravenous injection of 7 grains over a period of one min. This report refutes previous work which had shown that caffeine dilated the cerebral arteries. However, it may be the method and time of administration that has produced this contradiction. It is difficult to see how the EEG can improve following the drug if its mechanism is one of vasoconstriction.

35. On the influence of anticholinergic drugs on the EEG of recent closed craniocerebral injuries. — H. Lechner, University of Graz, Austria.

Our investigation was based on the findings of Bornstein whose experiments showed that free acetylcholine (ACh) could be demonstrated in the cerebrospinal fluid (CSF) after craniocerebral injury or after electroshock treatment (ECT). He was also able to correlate the gravity of EEG changes with the amount of ACh in the CSF. He concluded that free ACh plays a role in the causation of comatose states and also of the states of irritability in cases of craniocerebral trauma. He next attempted to counter these changes with atropin, in which he succeeded. Further, atropin was used in the treatment of head injuries with varying success (Ward, Marguth and Krenkel) but all writers agree that this drug is not the one of choice on account of its toxic effects.

We therefore made it our task to search for a drug capable of countering EEG changes in head injuries without producing too great side effects. Since it was known from experimental work (Jenkner) that scopolamin and N-diethyl-aminoethyl di-benzoparathiazine hydrochloride (diethazine HCl, RP 2987, casantin, Diparcol HCl) are able to change the EEG picture in monkeys after ECT and approximate it to normal, we decided to examine these drugs with respect to their effect on recent craniocerebral injuries.

All patients admitted during a certain period to the hospital with recent closed head injuries underwent EEG examination; recording of that derivation which contained the highest incidence of pathological activity was continued and either scopolamine as the hydrobromide in a dose of 0.6 mgm or Diparcol hydrochloride in a dose of 250 mgm. were given intravenously. In this way 83 cases were examined, a group of 46 cases receiving scopolamine and a second group of 37 receiving Diparcol. Further, 15 normals were examined, of whom 5 had scopolamine and 10 Diparcol.

In the first group there were 12 cases with a slight abnormality, 13 with a slight dysrhythmia, 1 with a medium and 2 with a serious dysrhythmia. Seven cases had suggestive and 10 pronounced focal findings and 1 case had intermittent paroxysms of generalised delta waves.

These EEG findings were changed by scopolamine as follows: *alpha* activity was reduced slightly in 3 and markedly in 5 cases; it was stabilised in 19 cases. *Beta* activity increased in 15 cases. *Slow* waves were augmented in 2, clearly reduced in 13 and stopped completely in 11 cases. In the controls, after the same dose of scopolamine, no certain changes could be detected.

The following changes were seen in the second group: slight abnormalities in 13, suggestion of a focus in 10, pronounced focus in 12, and intermittent paroxysmal delta waves in 2 cases. Injection of Diparcol had the following effects on these EEG's: *alpha* activity was reduced in 17 and its frequency lowered in 7 cases; it was stabilised in 6 and unchanged in 5. *Beta* waves were increased in 1 and reduced in 2 cases. Reduction of *slow* waves was brought about in 6 and their disappearance in 20 cases. Generalised delta paroxysms showed a distinct diminution. In all our controls there was a reduction of alpha activity; only in a single case was there an increase of beta activity.

Our investigation shows that the drugs used cause, in a certain proportion of cases of recent craniocerebral trauma, an approach towards normal of brain activity. This brings out some interesting aspects of the ACh metabolism in such head injuries, but their discussion would exceed the frame work of the present subject. It has been known for a long time, from the work of Jasper and his co-workers, that EEG changes provide a measure for the severity of head injuries and, further, it has been shown by Williams that EEG changes persist longer than clinical signs and symptoms. From these data it must be concluded that the use of drugs of the present group provide a new point of view for the treatment of craniocerebral injuries.

36. Profound EEG disturbances due to intolerance of anti-convulsant drugs. — J. Roger, H. Gastaut, H. Collomb and G. Miletto, Service Neuro-Psychiatrie, Marseille.

Observation of two similar cases treated with anti-convulsants for several weeks revealed a clinical intolerance signalised by astasia and abasia, accompanied by a profound EEG dysrhythmia with continuous delta and sub-delta components diminished by opening the eyes. The clinical and electrical disturbances disappeared after withdrawal of the medication, but reappeared when it was again exhibited. In one case the offending compound was sodium diphenyl hydantoinate and in the other 5-ethyl-5-phenyl hexahydropyrimidine-4: 6 dione.

37. Oculo-clonic responses in alcoholic intoxication and during treatment with nicotinic acid hydrazide. — G. Cardaire, H. Collomb and G. Miletto, Service Neuro-Psychiatrie, Marseille.

Oculo-clonic responses and recruiting responses, which are rather rare in chronic alcoholics, are found regularly at the onset of alcoholic delirium in various degrees and disappear with relief of the conditions. Similar responses are often seen during treatment with nicotinic acid hydrazide. Their appearance can be used to help predict complications in this treatment. These two findings may be related, and seem to support the suggestion of an analogy between the complications of alcoholism and those of izoniazide, such as polyneuritis and mental disturbances.

38. Action du méprobamate sur l'EEG humain. — G. Miletto, H. Collomb et G. Cardaire, Service Neuro-Psychiatrie, Marseille.

Cinquante sujets traités par le méprobamate à doses thérapeutiques habituelles (1 gr. 20 à 2 gr. 40 pro die) ont montré des modifications très minimes de l'EEG mais qui tendent toutes à un discret ralentissement de fréquence de l'alpha et à une augmentation d'amplitude. Avec des doses de 30 mgr/kg. on obtient une synchronisation assez accentuée avec apparition d'ondes lentes qui semblent signer un effet fonctionnel de mise au repos du système réticulé. Avec 60 mgr/kg., on obtient au contraire des rythmes rapides généralisés permanents accompagnant un état de somnolence. Dus à une action propre du médicament ils sont semblables aux rythmes rapides des barbituriques et probablement de siège et de signification analogue.

39. Inhibitory phases as an action of certain pharmacological substances, and the reflection of these phases in the EEG. — V. S. Rusinov and N. N. Burdenko, Institute of Higher Nervous Activity and Institute of Neurosurgery of the Academy of Medical Sciences of the U.S.S.R.

1. Phenomena investigated: changes in the electrical activity of the cortex of the hemispheres of the brain of human beings and of animals, following intravenous injection of substances used in the practice of neurosurgery (Novocaine and sodium Pentothal).

2. On intravenous injection of varying doses of Novocaine (from 10 to 80 ml. of a 1 per cent solution of Novocaine) which is used to free patients from persistent pain syndrome, the greatest changes in the electrical activity of the cortex of the hemispheres are observed in the course of the first 10-15 min. The alpha-rhythm is lessened in amplitude, a discontinuous inhibition of the alpha-rhythm appears. In some cases, after 6-7 min. an asymmetry appears in the EEG of the right and left hemispheres, due to a predominance of slow waves in one of the hemispheres. Before this phase of slow waves a phase of rapid fluctuations in the EEG is observed.

3. Rhythmic light stimuli, which before the introduction of the Novocaine evoked a following of the cortical rhythm to slow frequencies, ceased to evoke this reaction in the presence of Novocaine.

Thirty to 40 min. after the start of the administration of Novocaine, an alpha rhythm reappears which differs in character from the original one — it does not change under the influence of indifferent stimuli.

4. Changes in the electrical activity of the cortex and thalamus of rabbits were observed, on the introduction of 2-4 ml. of a 2 per cent Novocaine solution. In the presence of Novocaine a lowering in the amplitude of the "spontaneous" bursts of electrical activity is observed and paradoxical reactions to rhythmic light stimuli, which vary in frequency and intensity, appear. With light flashes of greater power the amplitude of the acquired rhythm is less than it is with stimuli of lesser power. After 40-50 min. a restoration of normal reactions is observed.

5. Under the action of sodium Pentothal, different phases in the state of the thalamus and cortex are very definitely expressed in response to sound and light stimuli.

During the phase of intensive stimulation of the thalamus, when frequent high-voltage discharges are registered on the EEG, a further following of the rhythm in response to 4-6 flashes per sec. is observed in the visual-and motor- cortex. At the same time there are no noticeable changes in the EEG.

After the phase of excitation of the thalamus comes to an end, a speeding-up of the rhythm in response to stimuli is observed in the cortex, and in the thalamus — a synchronisation in a 4-5 c/sec. rhythm (V.Y. Maiorchik).

6. Under certain definite experimental conditions, there appear in the rabbit two divisions, differing in their electrical activity, in the cortex of the hemispheres: an upper division, including the four outer layers of the cortex, and a lower one including the fifth and sixth layers.

With the use of pharmacological substances it was established that the reactions of these two divisions can proceed in a proportional relationship to one another, as the electrical activity of the upper division is intensified, the potentials of the lower division of the cortex are depressed, and vice versa.

Under the local action of acetyl-choline (a piece of filter-paper one square mm. in size, soaked in a 1 per cent solution of acetyl-choline, applied to the cortex for one minute) the corresponding sector of the cortex of the opposite hemisphere reacts promptly and strongly. In the EEG of this symmetrical sector of the cortex there appear high-amplitude sharp waves (acetyl-choline waves), while on the EEG of the sector of the cortex subjected to the action of the acetyl-choline slow fluctuations, much protracted in time, are observed (M.Y. Rabinovitch).

40. Current flow in the central nervous system. — Sir Bryan Matthews, Physiological Laboratory, Cambridge, England.

The potentials recorded between a single electrode in grey matter and a distant electrode may arise from a change of potential at a cell surface separating the electrodes (intracellular recording) or from a change of local current flow coming from sources and sinks on membranes not separating the electrodes (extra-cellular recording). Only the latter are to be considered here.

With a single electrode and a distant earth, the same event may be recorded as positive or negative or nil, depending on the position of the electrode relative to the source and sink.

Many authors have used pairs of electrodes to overcome some of the uncertainties introduced when recording against earth. Such a system records the component of the action current at the electrode site resolved in the direction of the line joining their tips. In a bulk conductor such as grey matter, the action current can, and in fact does, change its direction rapidly in the course of activity. An instantaneous record of the direction as well as the magnitude of the current in a given plane can be obtained by using a second pair of electrodes close to the first pair with the tips along a line at right angles to the first pair.

Then if the first pair deflects the X plates of an oscilloscope and the second pair deflects the Y plates, the spot will move in a way to show the instantaneous magnitude and direction of the action current in the plane of the electrodes. For the deflexion of the spot in each direction will be proportional to the action current component in that direction; the spot will thus describe the required polar diagram.

In practice the electrodes are Ringer-filled microelectrodes with 2-10 μ tips separated by 50-500 μ. They feed, through cathode followers, two similar differential amplifiers having a time constant of about one second and a discrimination against in-phase signals of 500 x. Time marking is provided by interrupting the beam at 1000 or 5000 c/sec. In the resulting record, the waxing and waning of stationary sources and sinks produces deflexion along a radius, whilst changes in the position of sources or sinks relative to the electrodes cause rotation of the radius about the centre. The local current is thus indicated in polar co-ordinates. It is impossible by other means to differentiate from a single record between activity changing in intensity and changing in position. At present the simultaneous analysis is made in two directions only; and a time-base record is taken by a second beam simultaneously. Information on activity in the third direction has been derived from successive analyses. It is possible to differentiate between local and general activity by small movements of the electrodes, the general effect remaining substantially constant over considerable distances. Many of the changes of physiological interest go down to the limits of detection. In some experiments metal electrodes have been used to lower the noise level, and filters are fitted which can be switched in to clarify slow changes at high amplification.

With any form of sensory or electrical stimulation, vector currents can be recorded widely from the spinal cord in the rat or frog, even outside the segment where impulses are entering. The pattern is constant for a given input, but changes greatly when impulses arise from different peripheral sites. The vector current at a chosen site is an integrated function of many sources and sinks at various distances from this site. It is well known that many central structures alter their activity when currents are made to flow in or near them artificially, and the orientation of these determines their effect; the naturally occurring vector currents may be expected to have parallel actions.

In many situations currents flow for long periods; these currents are carried by ions and the direction of transport of natural reagents is indicated by the current vector. The addition of a vector analysis to the normal record of focal potentials in the spinal grey matter enables a number of features of these to be readily interpreted.

41. Depth electrographic studies of the activity in the human brain and the effect of some drugs (including Mescalin, L.S.D. 25 and chlorpromazine). — C. W. Sem-Jacobsen, Gaustad Mental Hospital, Oslo, Norway.

This study was started at the Rochester State Hospital in 1952 in co-operation with the Mayo Clinic. The main workers have been Drs. M. C. Petersen, H. W. Dodge, J. A. Lazarte, C. B. Holman, and the author.

During the last five months I have continued the study at Gaustad Mental Hospital, Oslo, Norway.

The main technique is well known from several earlier publications. The size of the electrodes, however, has been steadily reduced. At present, we are trying out stainless steel, 20 microns in diameter. The paucity of demonstrable brain damage is pleasing and may be still less with the finer electrodes.

It takes usually three days after the operation before a baseline recording is obtained. Changes during the first days following the implantation of the electrodes may be due to anesthesia, other drugs and surgical trauma.

The various areas of the brain seem to have an easily recognizable activity. In the frontal lobe, a rhythmic 2-4 c/sec. activity is consistently found in the ventro-medial aspect and a 25 c/sec. fast beta activity is seen in the lateral aspect of the same lobe. Under the influence of ether, the frequency of the activity is increased. Under the influence of Pentothal, the frequency of the activity is decreased. However, this applies to the lateral fast activity, where there is an increase in the voltage of this activity so that it seems to overshadow all other activity in the earlier stages.

The rhythms in the olfactory bulb are demonstrated and under the influence of anesthesia the frequency of the activity changes in the same way as the lateral fast activity. Recognizable characteristic rhythms are seen in the motor area and underlying white matter. The fluctuation during sleep is seen in the lower part of the slide. The difference in response to touch and pain is recorded from the general sensory area.

From the auditory area and underlying white matter, the response to sound stimulation has been studied. It is possible to demonstrate the speed of the sound impulses. The effect of Pentothal on the response to trains of clicks are also illustrated. There is at first an increase of amplitude of the response, later there is a decrease in the duration of the response.

From the occipital lobe visual fast gamma activity and lambda waves as well as alpha activity are elicited, with a maximum voltage from their respective regions. The lambda waves seem most probably related to accommodation of the lens.

In the temporal lobe a quite different type of activity is seen and there is no clear-cut relation between this activity and somatic functions. On the other hand, in the psychotic patients there seems to be a relation between the activity in this region, the activity in the ventromedial aspect of the frontal lobe, regions of the parietal lobe and the hypothalamus. Reserpine does not seem to have any effect on this activity except when the dose is so large that there is a marked fall in blood pressure followed by altered level of consciousness.

Mescalin and L.S.D. 25 have been given to several patients. In one patient a double spike focus appeared, at the same time as the clinical effect of the drug. It was a focus firing with a peculiar type of double spike. The focus fired about three times per second continuously for hours. The changes in the record were undistinguishable, whether Mescalin or L.S.D. 25 were used. The EEG changes as well as clinical changes were quickly reversed by chlorpromazine i.v. The focus appearing in this patient was in the same general region as where spike foci have appeared in other patients at the time of acute hallucinated and agitated episodes.

42. The superficial spread of cerebral potential fields. Some evidence provided by hemispherectomy. — William Cobb and T. A. Sears, The National Hospital, Queen Square, London.

After the operation of hemispherectomy the EEG on the operated side is never completely flat. Though the potential changes there may be of the same order as those from extra-cerebral causes, in many cases there can be no doubt that an EEG is being recorded, at points 5 or 6 cm. remote from the nearest brain. In general it appears as a smaller version of the EEG of the intact side, following the overall fluctuations in frequency and amplitude with fair fidelity.

The spread of these potential changes from the intact side might be predominantly in skull and scalp or in fluid, or equally in both. That the fluid (C.S.F.) has about the same conductive properties as brain is suggested by the observation that the blink potentials usually remain symmetrical after hemispherectomy; it is possible, however, that they are conducted almost wholly in the skull and scalp, which could account for the lack of disturbance by blink potentials experienced in corticography and depth recording.

Recently a long-awaited opportunity of investigating the relative importance of the two media has occurred. In the course of a few months three of our hemispherectomy patients have shown signs of raised intracranial pressure, the investigation of which has required partial replacement of the fluid in the hemispherectomy cavity by air, so that it has been possible, by positioning the head, to compare the potential changes at an electrode with fluid or with air beneath it. These patients are seldom among the most cooperative and it is unfortunate that the best of them in this respect has a very low-voltage record, which gives no useful information. However, the results from one child, though limited, are clear; while they are similar in the third child the small amplitudes do not permit of confident interpretation on this evidence alone.

In brief, the activity at any electrode is larger when there is air under it than when there is fluid; there are also differential effects, the slower waves (K complexes) being less affected than the faster.

To check these results hemispherectomies have been performed on anaesthetised cats. The operation has been done through the smallest possible frontal craniotomy with minimal disturbance of the scalp; then, with the nose elevated, Ringer's fluid could be run into, or sucked out of, the cavity at will. It was hoped to use the cortical response to light flashes as the signal, but when recorded from the scalp these were too small to be useful, though of normal size when later recorded from the exposed cortex. Accordingly, three wires, insulated except for their tips, were inserted through frontal drill holes on the

intact side to form, by pairing, three dipoles in different planes, approximately in the region of the visual cortex. A sinusoidal input of 75 mV. to either of these dipoles gave a maximum of 55 μV. at a pair of scalp electrodes. It was found that the substitution of air for fluid might, at any particular pair of electrodes, either increase or decrease the P.D., or its sign might even be reversed. A very small addition of fluid to the air-filled cavity, such that there was still air under the relevant electrodes, might have this result.

It is clear, therefore, that the effect is essentially one of changing the shape of the potential field, which would account for the differential effect on the two components in the human case, assuming that their sources were not identical. It is also clear that considerable conduction is possible in the plane of the tissues overlying the brain, and this is a factor which must be taken into account when interpreting the EEG of the whole, as well as of the half, brain.

43. Some observations upon stimulation of the hippocampus in man. — G. Pampiglione and M. A. Falconer, Department of Clinical Neurophysiology, Institute of Psychiatry and Guy's-Maudsley Neurosurgical Unit, London.

Direct electrograms were obtained from the superior surface of the hippocampus in 17 conscious patients operated under local analgesia. The brain was exposed by a lateral craniotomy 12 times on the left and 5 on the right. After preliminary corticography an oblique incision about 2 cm. long was made in the middle temporal gyrus about 5-6 cm. behind the pole opening into the temporal horn of the lateral ventricle. Under direct vision through this incision a silver-silver chloride ball electrode (1 mm. diameter) was slid over the anterior portion of the hippocampus, the walls of the temporal horn keeping the electrode and its insulated flexible lead in place. A second electrode of the same type was placed over the superior surface of the hippocampus from 2 to 3 cm. behind the first. Other electrodes were placed over the surface of the lateral aspect of the exposed temporal cortex in front of, and behind the cut and over the exposed frontal and parietal lobes. Other electrodes still were slid under the orbital frontal cortex, on the temporal pole, the uncus, the anterior and the posterior part of the hippocampal and/or fusiform convolutions. Scalp electrodes had been secured prior to operation over the contralateral hemisphere in the mid-temporal, posterior temporal, frontal and parietal regions.

This arrangement was devised in order:

1. To ensure that the electrodes in the depth were actually in contact with the superior surface of the hippocampus with but little disturbance of the brain in its immediate proximity.

2. To record the spontaneous activity of the hippocampus simultaneously with that of the cortex of the hippocampal convolution, temporal pole, uncus and other regions of the brain when their connections are still intact.

3. To collect data on the subjective and objective phenomena evoked by the electrical stimulation of the hippocampus in conscious patients.

The stimuli used were 50-60 per sec. square wave pulses of 3 msec. at 3-4 V. (occasionally 6-10 V) applied through the electrodes placed on the hippocampus for periods of from 2 to 10 sec. No attempt was made to establish ''threshold values'' for either discharges and/or clinical phenomena, our aim being to evoke clinical responses without preliminary alteration of the ''excitability'' of the area.

All our 17 patients were suffering from seizures deemed to be of temporal lobe origin and were going to be submitted to temporal lobectomy. Each one had shown over a period of several months to several years, definite EEG abnormalities mainly in the temporal regions. In each patient stimulation of the hippocampus was performed at least twice (up to 6 times) without displacing the electrodes, the intervals between stimulations varying from 5 to 20 min., with a total of 53 stimulations. The temporal lobe later removed in one piece including the uncus and the anterior 3-4 cm. of the hippocampus was studied histologically by Professor A. Meyer and Dr. J. Cavenagh.

The clinical and electrographic features varied a great deal from one patient to another, and even in the same patient for similar parameters of stimulation. On no occasion did a major seizure occur, even when 10 V. were applied. No constant relationship was found between the duration and pattern of the electrical changes and the type and duration of subjective and objective clinical phenomena. Clinical phenomena closely similar to the patient's spontaneous aura or attack were evoked on some occasions, including ''peculiar sensations'', complex hallucinations, ''dreams'', apparent confusion, speech disturbances. On other occasions the clinical phenomena were of a kind apparently different from the patient's spontaneous manifestations. Olfactory hallucinations were very rare. Sometimes no clinical changes were noticed in spite of prolonged electrical storms being induced; and at other times the clinical phenomena outlasted the electrical changes recorded.

The distribution of the evoked discharges was less variable, and on no occasion were gross changes seen in the orbital and lateral fronto-parietal cortex or in the contra-lateral temporal scalp records. Often the discharges were limited to the areas of one or the other, or of both electrodes placed over the hippocampus. The temporal pole, the uncus, the hippocampal and fusiform convolutions were also often involved either with or without participation of the anterior half of the lateral aspect of the temporal cortex. The temporal regions behind the level of the cortical incision were less often involved.

Some illustrative examples will be presented for discussion.

44. Multi-channel recording and polygraphy as an aid to EEG. — H. Fischgold, G. Arfel and P. Mathis, Hôpital de la Pitié, Paris.

1. During the last few years there has been a tendency in France to increase the number of channels in EEG instruments. From 6 to 8, the number has gone up first to 10, 12 or 15, even up to 22.

We propose to describe the application of an apparatus with 30 channels — 22 for the EEG and 8 for recording other variables (breathing, pulse rate, blood pressure, PGR, Drohocki integrator).

This equipment has been in use for three years at the Hôpital de la Pitié.

Another 20 channel machine is working at the Centre Hospitalier Foch.

2. Multiplication of channels up to 20 or 22, raises serious problems but it has been found useful in the location of focal abnormalities.

Special devices for orientation analysis and location, worked out by one of us (Mme Arfel), will be described.

3. Polygraphic recording has permitted special studies of sleep, coma and petit mal.

A description of these results has already been given at the Marseille Colloquium. On this present occasion will be added some hitherto unpublished observations on reaction times and the PGR.

45. Multiplication des plumes en routine EEG. A propos d'un appareillage à 20 dérivations en service à l'Hôpital Foch de Suresnes (France). — Madame G. ARFEL-CAPDEVIELLE.

Cette note expose la méthode d'utilisation d'un appareillage à 20 dérivations, *destiné essentiellement aux examens de routine* et accessoirement à la recherche.

La méthode est avant tout fondée sur l'intérêt des montages à « *courtes* » *distances interélectrodes* (5 cm. en moyenne), particulièrement profitables lorsqu'un grand nombre de territoires cérébraux peuvent être simultanément explorés.

Pour qu'un appareillage aussi complexe soit aisément maniable et afin de faciliter *l'analyse visuelle* de tracés dont les larges dimensions peuvent entraîner une dispersion de l'attention, nous avons jugé utile:

1° *d'instituer des montages aussi simples que possible* où les territoires symétriques soient facilement repérables, ce qui permet en cours d'enregistrement ou d'interprétation d'évaluer rapidement les éléments comparatifs;

2° *de standardiser* non seulement les montages des examens courants, mais aussi ceux destinés aux localisations.

La méthode comporte en effet:

Les examens courants, faisant appel à 21 électrodes et comprenant 4 montages de base et 2 montages de complément. Ces montages, dont les plus importants sont un montage longitudinal et un montage transversal à courtes distances, réalisent une sorte de quadrillage de la convexité crânienne qui conduit à une analyse spatiale très complète.

Les conditions pratiques indispensables à leur bonne réalisation sont exposées.

L'examen courant doit durer au minimum 30 min.

Les examens particuliers qui nécessitent 31 électrodes réduisent le champ des investigations à un *seul* hémisphère ou à des régions *symétriques* des deux hémisphères. Ils utilisent aussi bien la méthode bipolaire que la méthode référentielle.

Dix montages de localisations « préfabriqués » ont paru pouvoir répondre à toutes les éventualités.

Ces montages — de même que ceux des examens courants, soit 16 en tout — sont pré-établis sur combinateur-pilote, ce qui rend leur utilisation extrêmement simple.

L'enregistrement simultané d'un grand nombre de territoires cérébraux par les montages bipolaires à courtes distances réalise une *étude très précise des particularités régionales, physiologiques ou aberrantes.*

La mise en œuvre de montages toujours semblables permet de réaliser dans des *conditions rigoureusement superposables* les études comparatives des lésions localisées, rendant ainsi plus significatives leurs similitudes ou leurs dissonances.

46. An integrating topograph. — A. RÉMOND, Faculté de Médecine, Paris.

We have previously described a so-called topographic method of recording electroencephalograms based on a novel method of re-arranging classical EEG records. Instead of presenting these latter, as is usual, in succession on a single ordinate, they are arranged so as to appear side by side, parallel to one another, in such a way that the centre point (or isoelectric point) of each derivation is projected on the same abscissa. In the course of a recording the respective position of the various derivations is inscribed at each instant on a contour which corresponds to the potential gradient from the electrode pattern being studied.

The first embodiment of this method of displaying the electrical activity of the brain may be called "analytical"; a contour is photographed every 1/100 or 1/1000 of a second, the set of records with respect to time showing the changes of this contour from one fraction of a second to another.

More recently we have used a novel version of the above topographic display which one could call "integrating" to distinguish it from the preceding one. The potential differences produced by a conventional EEG are collected, during the very short time necessary for sampling them, only after the application to the subject of a sensory stimulus. At the same time as the value of these PD's appears on the screen of a C.R.O. a quantity of electricity corresponding to it is accumulated in a convenient storage circuit. Since the PDs build up always in the same time relation to the regular stimulus it is evident that each repetition tends to augment the stored values in proportion to the contribution from the response to the stimulus; the components corresponding to the spontaneous electrical activity are always randomised with respect to their own time relations.

The persistent image which forms on the CRO by the accumulation of charges is then amplified at each repetition but above all changes progressively in wave-form. This transformation is made at first in an apparently random fashion, but then approximates more and more closely to the ideal contour which represents the average evoked topographic response in the region studied, all spontaneous activity being eliminated. According to the relative predominance of components due to the response in the total activity, the number of repetitions can be selected between several hundreds and several thousands. An evoked signal of a few microvolts can thus be observed quite easily against a background of "brain noise" of several tens of microvolts.

The circuit we are using enables us to select between one millisecond and one second, the time interval between the stimulus and the sampling operation; the experimental procedure is to explore successively the response corresponding to various significant latencies and thus to record a family of curves corresponding to regular displacement in time, from the same set of active electrodes.

The apparatus at present in use employs 8 channels since it is connected to an 8-channel EEG. We are using it for recording one after the other from straight lines of electrodes symmetrical on the two hemispheres and for exploring in succession the various parallel electrode chains necessary to explore the surface of the scalp in relation to a given sensory area. The C.R.O. record corresponding to each in-

tegrated response may be photographed but can also be recorded on tracing paper before being erased to give place to a fresh recording.

47. Conditioning fields. — CATHERINE POPOV, Laboratoire du Conditionnement, Hôpital de la Salpêtrière, Paris.

At the Marseille Congress in November 1955 we showed how the notions of dominance, cyclochrony and repetitive properties of the brain were leading us to a more precise idea about the nature of the phenomena which come into play during conditioning. In order to throw into relief the modifications which we believe should be made in the classical theory we used the traditional arrangement of stimuli for the experiments reported in Marseille (the first part of our paper). Henceforth, however, we are inclined to assert that the arrangement of the stimuli does not play an essential part in the building up of conditioned responses, if it is not that of determining the pattern of the visible cycle. The notion of ''conditioning fields'' to which we have resorted takes account of this assertion, and this notion is the subject of this paper.

When one provides an absolute (dominant) stimulus of sufficient intensity it may be adequate to set up in the corresponding region of the brain a zone of enhanced excitability. If a so-called indifferent stimulus occurs a little later, it may reproduce, according to the rules of dominance, the simultaneous and consecutive effect of the absolute stimulus. A few successive repetitions of the indifferent stimulus given alone result in its conditioning. Still further repetition of such stimulation results in the progressive and total extinction of its acquired effect, suggesting that we are indeed dealing with a conditioning process.

This observation demonstrates the transient character of these zones of enhanced excitability which appear at the functional level of the cortex, an attribute which is opposed to the inertia of dominance.

This extremely simple form of conditioning is set up much more quickly than the classical type, and it seems to us to be the most likely sort of event in the life of a living creature.

48. Rhythmic activity recorded in the reticular formation of the brain stem during conditioning in the cat. — N. YOSHII, H. PROVOT and H. GASTAUT, Faculté de Médecine, Marseille.

Permanent electrodes were implanted in 4 cats either in the skull or in the thalamus (anterior ventral nucleus, centro-median of Luys) and in the reticular formation of the brain stem. The EEG studies of conditioning were conducted for one to two months. The continuous auditory conditioned stimulus precedes and overlaps the unconditioned stimulus represented by rhythmic flashes of light repeated several times a second. After a few days the auditory stimulus, though at first ineffective, begins to modify the electrical brain activity.

The first effect is an evoked potential followed by generalised de-synchronisation, later a repetitive response appears related in frequency to the unconditioned flicker.

This repetitive response lasts not only during the application of the conditioned stimulus but also apart from this; it takes the form of spontaneous bursts of considerable duration (some seconds to several minutes) of large regular waves with a frequency which approaches more and more closely to that of the rate of the flicker.

In one case in which this ''spontaneous'' rhythm at 5 c/sec. appeared from the beginning of the experiment in a cat stimulated daily at 5 f/sec., we changed the frequency of stimulation and used flashes at 10 f/sec. After only a day there appeared in the reticular formation a burst of rhythmic activity at 10 c/sec. which, as it were, competed with the 5 c/sec. rhythm. A few days later this rhythm had become dominant in large bursts. We consider it important to emphasise that these spontaneous rhythms related to the frequency of the light stimuli appear only in the sub-cortical structures and mainly in the brain stem reticular formation. Their appearance in the occipital cortex is unusual and assumes the form of bursts accompanying those recorded in the brain stem. It is also important to realize that these spontaneous rhythms are the same as those which appear during the application of the conditioned stimulus and which therefore constitute the conditioned response. We believe that we can assert that these repetitive discharges at the specific frequency correspond to a conditioned response not only to the auditory stimulus but also to the general conditions of the experiment. We think we can even put forward the hypothesis of a memory trace; the reticular formation in the general framework of the centrencephalon has after all been suggested by Penfield as the essential site of memory.

With regard to the rhythmic appearance of this memory trace, this has been considered by Grey Walter who, in 1950, underlined the advantages of an oscillatory theory of memory and concluded: ''until there be some evidence to the contrary, I shall continue to support a working hypothesis which includes the proposition of rhythmic oscillation between cerebral elements as a physical basis of short-term memory.''

49. The mechanism of potentials evoked in the occipital region in human subjects by saccadic movements of the eyes. — H. and Y. GASTAUT, Faculté de Médecine, Marseille.

Certain subjects who show large occipital spikes when the eyes are open are asked to scan the outline of a window 3 metres square, brightly lit and 2.5 metres away. The saccadic movements of the eyes are recorded as deflections whose sense and size indicate the direction and extent of ocular movements; the very short rising phase of these deflections corresponds to the eye movement proper while the much slower falling phase corresponds to the following period of fixation. It is thus easy to measure the duration of the saccadic movements (45 ± 5 msec. for an angle of about 15°) and of the pauses (220 ± 70 msec.). These values agree with those put forward by other workers, notably by Valentine (1953) and Morel et al. (1954).

In the most favourable conditions one can observe a few occipital spikes without corresponding saccadic movements and vice-versa, but the general rule is correspondence of the two phenomena which accompany the exploration of one or several sides of the window. (Always the same ones in the course of several successive explorations.) Each eye movement precedes the occipital spike by 70 to 80 msec., suggesting that the latter is a potential evoked either

by an afferent volley in the visual pathways set up in the retina or by proprioceptive afferents from the occulomotor muscles. Of these hypotheses, the latter is untenable since the occipital spikes disappear, while the movements persist, when the subject tries to follow the imaginary outline of the window in total darkness with the eyes closed.

Considering that the latency of the occipital potentials evoked by a flash of light is about 80 msec. (Cobb and Morton, 1953) and that the occipital spike occurs at 70-90 msec. after the beginning of the eye movement, it seems likely that the latter produces an augmentation of afferent visual signals by variation of retinal illumination, resulting from the scanning of a non-uniform field.

To check this hypothesis we have taken records from subjects watching motion pictures, a situation which we have already shown tends to increase considerably the number of occipital spikes. The film used always contained short sequences of which some avoided saccadic movements (by forcing fixation on a stationary object or by compelling the eyes to follow smoothly a slowly moving object) while others encouraged the movements (by provoking alternating displacements of the eyes toward several stationary objects, or by producing a true opto-kinetic nystagmus along a row of objects). In these conditions it appears that scenes of the first type do not evoke occipital spikes, while those of the second type do provoke numerous ones.

It would seem therefore that the majority of occipital spikes when the eyes are open should be accepted as representing potentials evoked by high frequency afferent volleys in the visual pathways produced by abrupt variations in retinal illumination accompanying saccadic eye movements. Such a mechanism does not of course exclude others likely to cause sudden retinal stimulation, for example blinking of the eyes as suggested by Evans (1953). It should not be forgotten, in fact, that the pattern in question is only found in subjects who show cortical hyperexcitability seen as large scale responses to flicker. (Y. Gastaut 1951). It is accordingly logical to suppose that any condition in which the afferent visual signals are liable to abrupt changes may provoke occipital spikes in a subject with over-excitable neurones, but it is considered that of all these conditions saccadic eye movements are the most important.

It is furthermore reasonable to assign particular significance to the hypersynchronous discharges of the occipital neurones which accompany eye movements and which should appear in all subjects, even when the hypersynchrony is too small to permit observation of the evoked potential through the skull. We suggest, in fact, that this local hypersynchrony (practically a miniature epileptic discharge) may have the effect of suppressing vision during the brisk eye movements which displace the optical image suddenly across the retina and which would otherwise cause marked blurring of the image. The classical psychophysiologists were satisfied that this blurring goes unnoticed because of the rapidity of the ocular movements; we prefer our hypothesis which invokes an interference effect to explain the absence of blurring during saccadic movements which may last 50 msec. for pauses of 200 msec. and which may therefore take up as much as one fifth of the effective viewing time.

50. The EEG-magnetograph and the EEG-spectrograph, apparatus for fast poly-analysis. — D. H. Bekkering, Medical Physical Institute, National Health Research Council T.N.O., The Hague.

By poly-analysis is meant the simultaneous frequency-analysis of more EEG channels. The analysis is fast because the time resolving power of the analyser is of the order of magnitude of one sec., this is the response time of the used bandpass filters. The EEG magnetograph is a magnetic tape recorder, which records eight EEG channels in one track. By playing back and analysing the eight channels successively and rearranging the results in the time, it is possible to have the disposal of the frequency-content of maximum eight EEG channels simultaneously. The EEG-spectrograph is a panoramic analyser adapted both for visual display and photographic recording.

The EEG-magnetograph consists of: input circuit, oscillators, modulators, recording amplifier, tape deck, band-passfilters, demodulators and output circuit. Amplitude modulation is used. The limiting factor is the noise on the tape.

The EEG-spectrograph consists of: input circuit, band-passfilters, rectifiers, gated tubes, electronic switch, master oscillator, timebase, output amplifier, cathode ray tube and recorder unit. The histogram is displayed 300 times per sec. on the screen of a cathode ray tube. This gives the impression of a continuously changing histogram. The recorded spectrograms resemble ''visible speech''. A spectrogram consists of 20 parallel lines, each line corresponding with one of the filters of the analyser. The occurrence of frequencies in the EEG is manifested in the spectrogram by an increase in blackness of the corresponding lines. A drawback of this type of recording is that the amplitudes of the frequency components are only qualitatively determined.

The EEG-spectrograph is especially of use if one is interested in time relationships concerning the frequency-content of the EEG. The profit of the poly-analysis is that with this system it is possible to study the frequency-distribution of several EEG-channels simultaneously.

Examples of this way of frequency-analysis will be shown.

51. Example of the use of the spectograph and the magnetograph the "squeak" phenomenon. — D. Bekkering, A. Kamp, W. Storm van Leeuwen and P. F. Werre, Medical Physical Laboratory of the National Health Organisation, and Electro-neurological Department, Neurological Clinic, University Hospital, Leiden.

In 1935 Durup and Fessard described that the alpha rhythm often begins with a high frequency. The frequency descends in ½-1 sec. to the dominant alpha frequencies. This phenomenon was described also by Cruikshank. Later W. Grey Walter called it a ''squeak'' in analogy with a similar frequency-change of sound.

When examining normal subjects with the spectrograph the phenomenon was observed in most subjects.

In the spectrogram the ''squeak'' has a typical aspect. The ''squeak'' does not occur at each eye-closure nor in all leads in which alpha rhythms were recorded. The latter could be studied only when

simultaneous spectrographic analysis of various leads became possible by the aid of the magnetograph.

To see how the squeak phenomenon develops topographically in some subjects, simultaneous spectrographic analysis was carried out of leads with short interelectrode distances. A row of electrodes, 2 cm. apart was placed in a line from the occiput to the temporal bone (right side of the head). In accordance with others more than one alpha rhythm could be observed. In our subjects the ''squeak'' was observed best in the occipito-temporal region. The highest frequencies of the squeak are observed in one or two of the leads only. As the frequency decreases, the field within which it is seen spreads frontally while the amplitude increases. Often the frequencies tend to decrease a little during 1-2 sec. after the ''squeak'' is over. In these cases, the region over which the alpha rhythm spreads is extended farthest frontally when the frequency is lowest. When the frequency rises the extension decreases again. This suggests that the ''squeak'' phenomenon may be explained by assuming that the alpha rhythm begins in a small region at a high frequency and as the alpha region extends, the alpha frequency decreases. Or, in other words, that the alpha rhythm starts with the synchronisation of few elements and as the synchronisation extends the frequency decreases.

52. The development in time and space of excitation and inhibition processes during conditioned EEG responses. A study based on the simultaneous automatic frequency analysis of several channels. — H. Gastaut, W. Storm van Leeuwen, A. Roger, H. Regis, D. Bekkering, A. Kamp and J. P. Werre, Service Neuro-Psychiatrie, Marseille, and Neurological Clinic, University Hospital, Leiden.

The actual experiments were made in Marseille and recorded on ferrotape to be played back and analysed in Leiden. The results reported, as an example of the technique, were obtained in a man with an occipito-parieto-temporal alpha rhythm and a Rolandic ''rythme en arceau''.

1. Before being used as a conditioned stimulus, the sound repeated several times at first produced a generalised blocking of the alpha rhythm, which effect rapidly disappeared (habituation).

2. The unconditioned stimulus was a light serving as a signal for clenching the right fist according to previous instruction. The complex stimulus invariably produced a generalised blocking of the alpha rhythm and of the ''rythme en arceau''.

3. Repeated combinations result in the rapid appearance of a process of conditioned excitation which is quickly submerged in a surge of internal inhibition provoked by the repetition of the combinations at long regular intervals (supra-maximal inhibition):

(*a*) during the application of the sound the process of conditioned excitation takes on at first the aspect of a general blocking of the alpha rhythm and of the ''rythme en arceau'', then that of blocking of the ''rythme en arceau'' only; this migration of the occipital focus of excitation towards the Rolandic region corresponds no doubt with a process of concentration of excitation in the region of the analyser related to the signal endowed with the greatest biological significance. Later on, the conditioned blocking of the Rolandic rhythm disappears in its turn as the effect of inhibition;

(*b*) during the interval between stimuli the process of supra-maximal inhibition is seen first as a re-inforcement of both the alpha rhythm and of the Rolandic rhythm, then as a progressive diminution and disappearance of these basic rhythms which are replaced by slow activity tending steadily towards the appearance of a sleep record;

(*c*) during this phase of inhibition the conditioned stimulus produces an awakening reaction which is re-inforced during the application of the unconditioned stimulus and takes on the aspect of a brief return of a ''squeak'' of alpha rhythm and Rolandic rhythm with concomitant disappearance of the slow waves. When the inhibition increases still further, this awakening reaction does not appear any more, except as an effect of the unconditioned stimulus, that is, during the presentation of the light which always produces clenching of the first. A sound different from that of the conditioned stimulus also produces an awakening reaction which is accentuated at the moment when the light should have appeared during a normal combination. This is an instance of conditioning by time interval, which is seen again as a spontaneous awakening reaction some seconds before the application of each combination.

The simultaneous automatic frequency analysis of several channels clearly displays the fluctuations in excitation and inhibition during electro-cortical conditioning, as well as their reciprocal relationship with respect to time and space.

53. Methods of measurement of the EEG. — V. A. Kozhevnikov, Laboratory of Physiology of Auditory Analyses, I.P. Pavlov Institute of Physiology — under Academy of Science of U.S.S.R., Leningrad.

1. The object of analysis and measurement of the EEG is to transform complex and multiform oscillograms into a comparatively small number of figures or graphs which will contain the maximum possible amount of useful information needed for the solution of the experimental problem posed. The measuring techniques used must do away only with unnecessary information which can be looked on as noise (Vogel and Grey Walter 1951; Woodward 1953). The variety of experimental problems being dealt with leads inevitably to a great variety of methods having to be used for analysing and measuring the EEG.

This report is concerned with techniques and apparatus evolved to ensure the automatic performance of the basic operations of measurement of complex biological currents; the discovery and separation of definite rhythms in the EEG and the measurement of their frequency and amplitude.

2. The main element of the equipment here described is a system of electronic band filters. The width of the bands of the separate filters correspond exactly to the frequency limits of the respective rhythms of the EEG. The main points of difference between such a system and the arrangement of filters usually employed in analysers can be summed up as follows:

(*a*) the output of the filters directly characterises the corresponding rhythms of the EEG, which represents a definite approach towards the expression of the result of analysis in biologically significant terms (O'Leary and Bishop 1951);

((*b*) due to the comparatively large band width of each filter, evaluation of the time dynamics of the rhythms is to a large extent still possible;

(*c*) thanks to the steepness of the sides of the frequency response curves, high selectivity of the filters is assured. This helps to separate out distinct rhythmic components of the EEG even when there is a high level of noise created by the fluctuations of other frequencies;

(*d*) it is possible to separate out fluctuations in any field of the infra-sound and sound ranges, since it is easy to alter the adjustment of the filter parameters;

(*e*) the stability of the characteristics of the filters does away with the necessity for constant tuning and calibration of the analysers.

3. Measurement of the amplitude of the fluctuations of the original EEG and of the isolated rhythmic components is carried out by means of linear detectors which ensure true representation of wave amplitude and of electronic integrators. The latter measure the average amplitudes of the signals being studied. The data are presented in the form of marks on a general oscillogram and on numerical counters. This makes it possible to carry out measurements both over short periods of time and over periods of any length desired.

On measurement of an unanalysed EEG data are obtained which are analogous to the definition of overall bioelectrical activity (Drohocki 1938). Integrated measurement of the output of the band filters gives results which are usually taken into consideration in experiments using frequency analysers as the overall activity for a number of resonance filters relating to this or that rhythm (Glasser 1954). In this case, however, the measurement is distinguished by greater accuracy and is obtained immediately in numerical expression.

For measurement of changes in the amplitude of fluctuations of the alpha-rhythm in connection with external stimuli, an integrator with needle indicators is used. This device is controlled by a time relay and measures the background alpha-activity and its changes at the moment of stimulation and afterwards.

A permanent record of the spectrum of wave amplitudes of the EEG and its components is obtained by means of a simple photographic method, based on using modulation of the bright mass of the ray of a cathode oscillograph with simultaneous displacement at right angles along the x-axis.

4. For continuous measurement of the frequency of waves there is an electronic timing device producing impulses whose amplitude is proportional to the duration of the fluctuations being measured. With the use of selection amplification and subsequent intensification of the impulses by the apparatus, it is possible to discover and register very small deviations in frequency (up to 1/1000).

5. The use of a system of direct numerical readings enables one to carry out long and continuous measurements of EEG without using an oscillograph. In order to check the accuracy of the readings it is useful to employ an encephalophone with a modulator, whose distinguishing feature is that it can be used for the simultaneous reception of both low and high frequency fluctuations of biological currents.

6. From the point of view of practical use, the most rational way of designing and producing the system of apparatus described above would appear to be:

(*a*) separate sections, making it possible to combine and set up these in various ways;

(*b*) specialised portable appliances intended for use under clinical conditions.

54. Analogue analysis of the mechanism of visual excitation and inhibition during scanning movements of the eyes and rhythmic stimulation. — W. Grey Walter, Burden Neurological Institute, Bristol.

An electric model of nervous excitation inhibition and synaptic activity (*Nerissa*) described elsewhere permits analysis of most phenomena seen in peripheral nerves and monosynaptic relays and also suggests the simplest mechanism necessary to account for the effects of intermittent visual stimulation as described by Evans and the Gastauts.

Records will be shown to illustrate how, in a system with two inhibitory relays, rhythmic or intermittent stimuli produce a paradoxical reversal of action, equivalent to *inhibition of inhibition of inhibition*.

Even if the real mechanism is more complicated than this, such experiments illustrate how analogue solutions may help to elaborate rigorous working hypotheses and thus to suggest clear-cut physiological experiments. For example, experiments with the model suggest that the mechanism underlying the occipital spikes described by the Gastauts, and the "lambda waves" of Evans, may be closely related to the exaggerated effects seen as "photic activation" in epileptics.

55. Some reflections about the analysis of a complex signal. — G. Raoult, Faculty of Science, Clermont Ferrand (France).

Frequency analysis in EEG is an important problem and we are going to give some precisions on the mathematical point of view of the analysis of a signal that must possess the following qualities:

(*a*) The frequency domain is very vast, about 30 octaves, and the mean frequency is very low, about 12 herz.

(*b*) The analysis must be made on the spot, generally as the recording takes place.

(*c*) The transcription must be easily readable.

Integral and series development of a signal.

When one knows a function $y = f(t)$ in a variation interval from zero to infinity, one can put

$$f(t)=\int_{-\infty}^{+\infty} F(\omega)e^{j\omega t}d\omega \quad \text{and} \quad F(\omega)=\frac{1}{2\pi}\int_{-\infty}^{+\infty} f(t)e^{-j\omega t}dt$$

This is possible only if the function satisfies the Dirichlet conditions, that is,

First $f(t)$ possesses a finite number of maxima or minima,

Second, $f(t)$ possesses a finite number of discontinuities. Moreover, the integral $\int_{-\infty}^{+\infty}|F(t)|dt$ must be convergent.

These conditions, simple as they are, are not satisfied by the simplest curves, for instance, sines or cosines. In order to be able to develop the functions, one has devised a new category of function that is called a "distribution", the first example of which is the Dirac function. Beyond this we cannot go, as it would carry us too far in a new field of mathematical research.

The situation is quite different if we stay in a time interval O-T. In these conditions, it is *always* possible to develop in Fourier series that we write:

$$f(t)=\sum_{-\infty}^{+\infty} a_n e^{jn\omega t} \quad \text{and} \quad a_n=\frac{1}{T}\int_0^{+\infty} f(t)\,e^{-jn\omega t}dt$$

The only drawback is that the time T has a particular part and there is no connection between the co-efficient obtained for two different times T and T'.

We can notice that the development is in function of frequencies multiples of I/T, and it is possible to forget frequencies that really exist, as would be the case of a development of sine ω t between O and 3T/2; we should have frequencies 2/3T, 4/3T, 6/3T, and so on, and never I/T.

These reflections show us that we must be prudent when we speak of instantaneous frequency, or even dominant frequency, because all depends on the manner in which the mathematical analysis is made.

Physical Methods of Research.

Many apparatus have been devised and one has to interpret their results.

The first idea is to use resonators, mechanical or electrical, and many apparatus [1] have been made. One has to resolve a differential equation of second order with a second member. The difficulty is that this second member is not an analytical function, and it is not possible to know it entirely when one knows only a fraction. One must also multiply the second member by the H function of Heaviside, because for t negative there is no function, and that introduces an infinity of spectral components. Even if you multiply the frequency, you must take care of these effects for if frequency is multiplied, the Q factor must also be multiplied by the same co-efficient, and you can lose information in that transformation.

Modern theories of probability functions could help us. They introduce the correlation function, which is defined by the mean of the product

$$F(\tau)=\overline{f(t)\,f(t-\tau)}$$

and also the cross correlation function, which is written $G(\tau)=\overline{f(t)\,g(t-\tau)}$

The apparatus known as "lock-in" allows us to realise easily these two functions [2]. The point is that we can get free of the time T, that fixed for us the frequencies.

These theoretical considerations show us that any system can give interesting results, but one must be very prudent in the interpretation, and always refer to the mathematical principles that underlie them. Anyhow, the correlation function method seems to open easily the door to a great deal of research.

1 Grey Walter, **Elec. Eng. 1943**, 236; Grass, **J. Neurol.** I 1938, 521; Kaiser, Comm. Apparatus.

2 Manus. **Arc. Sc.**, Geneva 3, 1950, 19.

SOCIÉTÉ D'ÉLECTROENCÉPHALOGRAPHIE ET DES SCIENCES CONNEXES DE LANGUE FRANÇAISE

Paris, 28 et 29 mai 1956

Secretary: M. B. DELL

9 rue Jasmin, Paris XVIème, France

1 and 2. The organization of the normal and pathological electroencephalogram: cortical mechanisms regulation and reactivity. — C. G. Lairy and P. Dell (Paris).

This report will be published in extenso in the Revue Neurologique.

3. Electroencephalographic investigations on the cortical reactivity. Variations in the latency of the cortical responses to intermittent photic stimulation. — E. Crighel, R. Brosteanu and V. Nestianu (Bucarest).

Using an electroencephalographic method in unanaesthetised cats the authors have found that there is a cortical response to each stimulus and that the latency of this response varies within the train of a period of stimuli. The latency of the response to the first stimulus has an average value of 28.97 msec. For the 2 to 4 following stimuli this latency increased by as much as 95 per cent and then returned to the initial value. This again was followed by a period characterised by regular oscillations around a mean value and finally these oscillation became completely irregular. The standard deviation was about 4.49.

During barbiturate induced sleep and in the postictal period immediately after a convulsive attack, the average value of the latency diminished by as much as 54 per cent and the standard deviation by 60 per cent. During the state of increased cortical excitability after intake of cafein or pervitine, the latency values increased by as much as 396 per cent and the standard deviation by 200 per cent.

The cortical response is due to a synchronization of a cellular complex where interneurones play a predominant role. During the inhibitory state there is a simplification of the complex relationships and therefore a diminution of the latencies. During excitation, there are longer latencies which indicate a greater complexity of the cortical structure.

4. The constant of electrogenesis as an expression of the regulation of the electrical activity. — Zenon Drohocki (Paris).

The electroencephalogram was submitted to a quantitative analysis by systematic measures of its mean amplitude with the electronic integrator of Drohocki. These measurements were carried out in humans and in animals during wakefulness at in-

tervals of 1 sec. during periods of different duration. The results of these measurements were represented in histograms corresponding successively to periods of decreasing duration. Whatever the duration of these measurements, one always finds the same general characteristics. (1) All these distributions are normal and can be defined by their usual parameters. (2) The position of the maximum (mode) is constant in the same individual. (3) The mean of one individual does not change in any significant way. (4) The variance is always small. Every electrogenesis is therefore confined to a very small zone and grouped around a central and maximal value which is constant in one individual. The fact that the same principal of organization and the same parameters are found at every temporal scale, demonstrates the existence of a regulatory mechanism. Each territory seems to have its proper regulation which is well defined by the parameters of the amplitude distribution. Under the influence of small doses of certain drugs this regulation can be established at a level which is different from the normal one. This is evidenced by significant modifications of the mean and the variance, as well as by displacement of the maximum. Massive doses of these drugs destroy any regulation and this is evidenced by the disappearance of the normal distribution.

5. Rapid rhythms and reactivity of the EEG during surgical anaesthesia. — G. ARFEL-CAPDEVIELLE, G. VOURC'H, R. KERNEN (Paris).

The electroencephalogram was recorded during anaesthesias carried out in 98 general surgical operations, among which 12 major abdominal interventions of a duration varying between 2 hr. and 6½ hr. The electroencephalogram was observed from the preanesthetic period on until the post-surgical phase of re-awakening.

Among the several rhythms which characterised the usual anaesthesia, only the *rapid activity* will be the object of this report.

Its characteristics both from the morphological and topographical point of view, will be considered, as well as the reactions to different stimuli. These elements were studied in the different periods where this type of activity was manifest or presented the *predominant element of the record*: that is during the *induction* first of all, and then during stages of light anaesthesia in the course of the surgical interventions.

Two examples were given in this study:

1. A *simple* anaesthesia, in this case an ether anaesthesia, in which the different clinical stages are easy to evaluate (stades of Guedel).

2. A type of *combined* anaesthesia (induction: penthobarbital, maintainance of the anaesthesia at a light level: nitrous oxide, oxygen and intermittent administration of small doses of penthobarbital, Pethidine and d-Tubocurarine). In this type of anaesthesia rapid activity was recorded during the major part of the surgical intervention.

Different reaction patterns characterised the rapid activities observed during induction and during surgical intervention. During induction and most specifically during analgesia the rapid activity still reacts, though in a somewhat variable way, to exogenous stimulation only. During this period the patient appears to be conscious at least he retains certain possibilities of making contact with his environment. Past memory and temporal and spatial orientation are preserved, as well as special modalities of reaction. Only perception of pain is made obtused.

During the *surgical period* the rapid activities although morphologically similar to those seen during induction, do not show the slightest reactivity not even in response to most violent stimulations. The mechanisms through which the rapid activities are produced or excited are reviewed in reference to opinions of different authors and particularly to those which interpret the rapid activities as to be correlated to a transient hyperactivity of the ascending reticular system (Schneider, Rossi, Zirondoli, etc.). This hypothesis may be valid for the genesis of the rapid rhythm seen during induction but can hardly explain those seen during the surgical period.

6. Variations of the arousal reaction in patients with disturbances of vigilance. Diagnostic interest of asymmetrical arousal reactions. — H. BONNET and J. COURJON (Lyon).

The mode of reactivity to sensory stimuli allows to evaluate the degree of disturbances of vigilance and by this to estimate the intensity of the corresponding functional disturbance. These reactions are the same whatever the etiology of the coma: severe head injury, brain tumors, intercranial hematoma, tubercular meningitis or any encephalitic process.

In conditions which may be cured the mode of reactivity is of prognostic value. The absence of any reactivity is a major sign of the severity of the condition whatever the aspect of the spontaneous activity may be. Recovery is possible in certain cases but only in young subjects. The mode of reactivity resembling the patterns seen during deep sleep as characterised by reappearance of background rhythms, appearance of K-complexes or bursts of high voltage slow waves indicate a less severe disturbance and most often indicate that the process is reversible.

These different modes of reactivity can evolve quite rapidly in their time course. During the same recording one may observe frequent changes in the type of the responses to sensory stimuli. The repetition of the stimulus may finally lead to the extinction of the response and it is then necessary to use another mode of stimulation to produce a response. Most often, however, this leads to an augmentation of the reactivity and to a pattern more and more close to normal, that is to a desynchronization of the background activity. These rapid changes can be obtained with injections of novocaine, either by intravenous route or by infiltration of the carotid sinus.

When disturbances of vigilance are present, focal abnormalities tend to disappear and the risk is then real that, e.g. in the case of a head injury, an intercranial hematoma may not be recognised. In cases of brain tumor the localization and often even the lateralization of the process may sometimes then become impossible.

In those cases the asymmetry of the mode of reactivity becomes of capital importance, since localization may only be possible on the basis of such an asymmetry. The arousal reaction may be completely absent on the side of the lesion. More often, however, there is only an asymmetry in the type and morphology of the arousal reaction, affecting the frequency the amplitude and duration of the induced changes. On the side of the lesion the arousal reaction is then more abnormal and indicates that the mechanisms maintaining alertness are more disturbed in this hemisphere than in the other.

7. Topographical analysis of the reactivity of the electroencephalogram during sleep in small children. — C. Blanc, C. Dreyfus-Brisac, H. Fischgold (Paris).

Reactivity to auditory and cutaneous stimulation was studied in children from the new born age on to the age of 3 years.

Until the age of three months the responses are generalized and consist in a general flattening of the record or in diffuse bursts, or in responses showing two stages. After the age of three months these responses change. They become higher in amplitude, sharper in form appearing in the form of a slow negative sharp wave, particularly over the central region. They still remain generalized.

At the end of the 1st. year of life, there is a modification of these unspecific reticular responses. *A topographic organization of the reactivity* appears which was studied with the referential method of Goldman-Wilson. It is possible to observe either generalized synchronous responses or localized responses confined to rolandic or frontal regions, frontal and occipital areas, or in occipital areas alone. *In these cases the different cortical areas do not regularly respond together to each stimulation. The morphology of the responses is not the same for all the territories.* The responses in the rolandic region assume the form of sharp diphasic spikes of high voltage which occur either in an isolated or repetitive manner. The frontal responses more often have the form of slow sharp waves. The occipital responses consist of slow waves of variable morphology.

Variations in distribution of these unspecific electrical responses have to be considered in the light of physiological and anatomical data and are in relation with a topographical organization within systems of thalamo-cortical connections. The appearance of the topographical organization of the activity at the age of 2 years is probably the first expression that these systems begin to function and therefore corresponds to an important stage in the process of cerebral maturation.

8. Abnormal forms of arousal reactions in the infant. — C. Dreyfus-Brisac, C. Blanc, P. Kramarz (Paris).

The study of the electrical activity during sleep is an essential step in the investigation of cerebral activity in the infant. Often abnormal responses are recorded while the spontaneous activity during wakefulness and sleep may appear normal. These responses are abnormal due to their long duration (10 sec. to a minute or even more), their generalization and their abnormal amplitude (300-500 μV.). They sometimes are very slow showing a frequency of only 1 c/sec., quite monomorphous in their activity, or they may be more rapid (4-5 c/sec.) sinusoidal in form and rhythmical in character. The slow waves are sometimes associated with spikes. The essential characteristic of these discharges seems to be their repetitive nature which suggests the existence of a pathological disposition to self-sustained activity reminiscent of the characteristics of epileptic afterdischarges.

These abnormal responses are often encountered in very abnormal children (encephalopathy with or without epilepsy, mental retardation). They are then often associated with abnormal sleep tracings with high amplitude and monomorphous character. Abnormal electrical activity during wakefulness is not so often encountered in these patients. These changes are of great interest in children with rather mild involvement where they often constitute the only electrical sign of an existing abnormality.

The existence of such arousal reactions of a diffuse character, of high amplitude and repetitive in character are often recorded in children of 10 months to 2 years of age which recovered from meningitis and often suffered from febrile convulsions. These may be the expression of a cerebral reactivity with tendency to self-sustained activity.

These abnormal arousal reactions could therefore be considered as a means of physiological activation permitting to appreciate certain tendencies to convulsive attacks.

9. Electroencephalographic changes in relation with paroxysmal disturbances of consciousness of a cyclic type. Presentation of a syndrome of probably encephalitic origin. — Th. Kammerer, R. Rohmer, L. Israel and L. Singer (Strasbourg).

The authors present four cases which were observed during a period of at least three years. The cases suffered from paroxysmal disturbances of consciousness characterised by coma, or subcoma, episodes of confusion with excitation which were precipitated by emotional factors. The presence of neurological signs and especially the encephalographic disturbances which were very marked exclude the possibility of a purely neurotic, i.e. psychogenic process. One of the cases died and came to autopsy and signs of chronic encephalitis were found. The EEG changes in these cases reflect faithfully the disturbances of consciousness and constitute a good index of "destructuration". The association of clinical, electrographic and anatomical signs in these cases seems to constitute enough evidence that we are dealing with a nosological entity, which was hitherto not recognised as such.

10. Electroencephalographic study of some cases of hepatic coma. — R. Cloche (Paris).

This study concerns a group of patients which during the course of cirrhosis of the liver, presented comatose episodes. The EEG expression of these states which are characterised by extreme variability of disturbances of consciousness is often very peculiar.

In six patients which were examined during hepatic coma the following EEG changes were observed:

(*a*) A very rhythmical and regular delta activity.

(*b*) Complex and characteristic patterns made up of numerous elements of high amplitude and sharp character, often triphasic with a positive component.

(*c*) The high variability of these patterns with changes of the electrogram occurring from one day to the next.

(*d*) In subjects which were examined only when the coma cleared or in pre-comatose states with minor mental disturbances, there was often only a slow rhythm of the theta frequency band sometimes intermingled with some delta waves.

The interest of this study lies in its importance for the interpretation of the etiology of the hepatic coma which is still not clearly elucidated. It seems that this is a toxic coma. The relationships which may exist between these electrographic changes and certain biochemical disturbances are discussed, especially with the disturbances of metabolism of nitrogen containing compounds.

11. EEG studies in two cases of unconsciousness with prolonged insomnia. — P. MATHIS and H. FISCHGOLD (Paris).

The authors studied two patients who after a period of acute coma remained in a state of unconsciousness which was nearly total, but seemed to be incapable of sleep. They remained for a period of more than four months in a state of decerebration with widely opened eyes. The dissolution of the functions concerned with the relation to the environment, the impossibility to understand and to respond remained total, but these characteristics of the comatose state contrasted with an ocular syndrome which was that of vigility and with the abolution of spontaneous sleep.

The EEG tracing of the first patient which was taken with the eyes opened or half closed showed a periodical appearance of slow waves appearing in bursts which were bilateral and located in anterior head regions. Such bursts of the same monorhythmical character could be precipitated by auditory, nociceptive and proprioceptive stimuli. After intake of Largactil or Nembutal the lids drooped and there was an upward turning of the ocular globes as is seen in physiological sleep; the periodicity and reactivity of the electrogram were accentuated and the waves of diffuse projection were slowed down to 1 c/sec. and were accompanied by acceleration of respiration.

The second patient gave the impression of being anxious and suffering from pain, did not close her eyes, neither at day time or night time, and from time to time emitted piercing screams. Her EEG was flat. A psycho-galvanic reflex could however be recorded and there were responses to intermittent photic stimulation.

With Pentothal and Nembutal sleep could be induced. The eyes were closed, the facial expression became relaxed but the electrogram remained flat almost linear. Any cortical regulation, any periodicity or reactivity was absent, both with eyes open and closed, or during drug induced sleep. This proves that coma can be dissociated from hypersomnia and these two cases prove that prolonged loss of consciousness can go along with abolition of spontaneous sleep.

12. Electrographic studies of the degree of vigilance during a prolonged course of traumatic coma. — R. FAU (Grenoble).

The author reports on the observation of a patient with a severe head injury who two months after his accident came out of his coma and showed a constant oscillation between a state of semi-vigilance and a state of profound somnolence. The EEG was taken during the semi-vigilant state showed a permanent delta rhythm which did not react to stimulations. During somnolence the delta disappeared and a 7 c/sec. rhythm was present which did react to auditory stimulations. This patient was seen two months later. He was no longer somnolent but semi-alert and nearly demented. At this time his EEG was flat, completely disorganised and with an intravenous injection of chlorpromazine a 7 c/sec. rhythm appeared together with a normal reaction to different stimulations. This observation allows to compare the effect of spontaneous somnolence with the effect of chlorpromazine. In both cases the tracing tends to become more normal, whereas it is more abnormal when the state of vigilance increased. One can therefore describe three stages: (i) a stage of vigilance and maximum disorganization of electrical activity; (ii) a stage of very attenuated vigilance characterised by a delta rhythm, and (3) a stage of somnolence characterised by a physiologieal rhythm at 7 c/sec. The variations of the tracing with somnolence are therefore very different in a normal brain than in a comatose brain. Somnolence seems to be a physiologically different state from sleep and coma and seems to be, therefore, for the sick brain what the relaxed state is for the healthy brain. These facts allow us to understand why the action of chlorpromazine on the EEG is very different on a abnormal brain and on a normal brain.

13. Correlations between the pulse frequency and the frequency of the EEG (preliminary note). — CLAUDE LEROY (Statistical validation by G. MARCU) (Paris).

The author records in all his patients the EEG and the electrocardiogram (taken from left to right hand) simultaneously at rest. These studies were all carried out in mental patients. In this study only subjects were used who did not receive any treatment, since any therapeutic measures, especially "neuroleptic" drugs would considerably modify these correlations. The results are as follows:
187 cases of all ages:

Basic EEG Rhythm	*Average of the EKG in every group*
8	71.9
9.10	79.3
11.12	83.2
General Averages	
9.27	77.8
Standard Deviation	
2	11

Since the statistical study showed an important influence of the age, a group of 107 cases was sampled where the age ranged between 25 and 50 years:

Mean age	*Standard deviation*
34 years 6 mo.	*11 yrs. 4 mo.*
Mean EKG 82.3	Standard deviation 15.03
Mean EEG 10	Standard deviation 2.06

Bravais-Pearson coefficient: r EEG/EKG $= +$ 0.444 significant at .01 limits of confidence at Z of Fisher at .01: $\begin{matrix}0.564\\0.327\end{matrix}$

In this small sampling of patients no correlations with diagnosis can yet be made.

The frequency of the electrocardiogram is dependant upon the sympathic tonus which in turn depends upon the reticular system. The encephalogram (background activity) is also dependent upon these systems. We intend to record the respiration under the same condition and to re-examine a greater number of patients.

14. EEG studies of the processes of connection formation between a light stimulus and a sound stimulus in the cat. — M. JOUVET, O. BENOIT, J. COURJON (Lyon).

The electrical activity of the cortex and the subcortical structures was studied in cats with chronically implanted electrodes. Intermittent sensory stimulation followed the presentation of a continuous light stimulus.

The connection formation between the two stimuli was manifested by two phenomena: (*a*) the appearance of a generalised cortical and subcortical response to light in the form of spindles. This was a very unstable phenomena; (*b*) an important facilitation of the cortical responses to intermittent sensory stimulation. In no case was it possible to obtain a conditioned response to light on the auditory cortex which was at the same frequency as the intermittent sensory stimulation.

When a ''meaning'' was given to the intermittent sensory stimulation (through association with an electric shock to the paw) stable responses appeared:

(*a*) the light alone will then produce the onset of slow waves in cortical and subcortical structures;

(*b*) the action of differentiation, extinction and external inhibition upon the latter phenomena was studied.

It is probable that the reticular formation and the diffuse thalamic system play a role in these conditioning processes.

15. Conditioning of generalized hypersynchronous discharges in cats with epileptogenic lesions. — F. Morrell (Minneapolis) and R. Naquet (Marseille).

The authors studied the electrographic conditioning in cats with cortical epileptogenic lesions. The recordings were carried out by means of chronically implanted electrodes. The animals were unanaesthetised and placed in a hammock.

The conditioned stimulus was a continuous sound of feeble intensity and the unconditioned stimulus was a light which was delivered at different frequencies.

In animals with epileptogenic scars in the region of the gyrus lateralis the unconditioned stimulus provoked (i) an asymmetrical driving response in the occipital region; (ii) a hypersynchronous generalized response of an abnormal type which started in the occipital region where the lesion was placed, and which did not necessarily stop after the end of the unconditioned stimulus.

It is interesting to note that this response could be conditioned and that it followed the different modes of extinction, differentiation and restauration.

16. Conditioning of hypersynchronous discharges of the myoclonic type induced by Cardiazol injection into the cat. — R. Naquet (Marseille) and F. Morrell (Minneapolis).

Using the same technique of conditioning which was reported by Morrell and Naquet the authors tried to condition the hypersynchronous response of myoclonic and generalized character which was obtained by intermittent photic stimulation combined with slow injection of Cardiazol at 5 per cent.

The animals which were used were either normal or had an epileptogenic lesion. It was proven that it is possible to condition this response and that this response followed the laws of differentiation. However the level of optimal Cardiazol concentration is difficult to mai tain. When the level of Cardiazol concentration is too high differentiation of the response is no longer possible. The response is then also elicited by stimuli of an entirely different nature, and it cannot be considered any longer as a conditioned response.

The type of responses obtained were similar in both types of animals used, but it was more easily elicited in animals with an occipital lesion in which the Cardiazol facilitated the generalized hyper-synchronous discharges which occurred also spontaneously and confered to them a myoclonic character.

17. Supramaximal inhibition studied by electroencephalographic methods on the rabbit. — C. Popov (Paris).

This report deals with a study of supramaximal inhibition. This was observed after an intense stimulation, which in its intensity went beyond the optimal level for the excitation of the animal. Different stages which appear in the course of such inhibition, called ''stages of sleep'' were studied in animals, which were not prepared, by taking the electroencephalogram corresponding to every individual one of these stages. During supramaximal inhibition these stages follow each other in reverse order to that described by Pavlov for sleep. The EEG then showed the following aspects: quiet tracing, flat record, paradoxical stage and return to the initial pattern.

This study confirms the results obtained in 1954 in man where an entirely different method was used, consisting in presentation of consecutive images.

In the animal, the flattening of the record expresses as in man, the presence of one of the stages of inhibition. The profound and less profound paradoxical stages are evidenced by the apparent return of the spontaneous activity, which is, however, characterised by absence of responses to various stimuli. In the animal, these stages follow those characterised by a flattening of the record and correspond to the subliminal inhibition which was demonstrated in man. Moreover, in man as well, the appearance of spontaneous activity was observed, while the response to different stimuli were abolished or at least modified.

18. A topographical study of conditioned electroencephalographic reactions which occur independently, simultaneously or successively in different cortical regions in man. — H. Gastaut, A. and C. Jus, F. Morrell S. Dongier, H. Regis and A. Roger (Marseille, Lodz and Minneapolis).

The authors demonstrated that a sound previously ineffective in producing EEG changes produces a conditioned blocking of the contralateral rolandic rhythm (''rythme en arceau'') if the sound regularly precedes a somesthetic stimulus capable of producing an unconditioned blocking of this rhythm. The conditioned rolandic blocking is also obtained when the exteroceptive or passive proprioceptive stimuli are replaced by an active proprioceptive stimulus as represented by the action of making the fist on commands given by the experimenter. It is then observed that the blocking of the contralateral rolandic rhythm occurs somewhat earlier than the reflex conditioned motor reaction. It is also observed that the over-reinforcement of the motor reaction carried out according to a verbal method developed by Ivan-Smolenski, also reinforces the EEG reaction, which then no longer is only contralateral but becomes evident in the rolandic region of both hemispheres. Finally, it is possible to produce a conditioned blocking of the rolandic rhythm by instructing the experimental person to make the fist as soon as a light stimulus is given. An auditory stimulus is then delivered regularly before the light stimulus and acts as the

conditioned stimulus. Under these circumstances, it is observed that the introduction of light as a supplementary unconditioned stimulus does not necessarily produce a conditioned blocking of the occipital rhythm. If such a transitory blocking occurs, it predominates on the side of the hemisphere contralateral to the hand making the fist. The task of making the fist seems therefore to represent a biological signal of greater importance than the passive illumination of the retina and this seems to produce a formation of a dominant focus of excitation in the sense of Oukhtomski which interfers with the occipital focus of excitation.

The repetition of combined stimulation, the failure to reinforce the conditioned stimulus or the use of a new sound, induced the appearance of phenomena of supramaximal inhibition, of extinction or differentiation which in the EEG are expressed by a local reinforcement of the rolandic rhythm, before taking the form of a generalized slowing of the background rhythms (sleep tracing).

Simultaneous electroencephalographic studies of different territories therefore discloses in man the dynamic processes taking place in the cortex. This method allows to give objective evidence of the elaboration of temporary connections, and of the mobility of foci of cortical excitation and inhibition.

19. EEG conditioning of epileptic discharges and the concept of reflex-conditioned epilepsy. — H. Gastaut, H. Regis, S. Dongier and A. Roger (Marseille).

The authors attempted to condition the spike and wave and multiple spike and wave discharges unconditionally precipited by intermittent photic stimulation in photo-sensitive epileptics by using sound as a conditioned stimulus. In two patients with a photosensitive form of petit mal attacks, in which the absences and myoclonic jerks were favoured or precipitated by certain traumatic situations, conditioning was obtained after about twenty trials of combined sound-light stimuli. The discharges thus conditioned obeyed the laws of extinction, restauration and differentiation. The authors are of the opinion that these conditioned epileptic discharges are dependent upon inhibitory processes of an active character which are accumulated in the reticular formation and they consider this as supplementary evidence for the inhibitory mechanism of petit mal, a notion which was supported by one of them a long time ago.

On the basis of these two observations, and in view of all the clinical cases which the authors have observed personally or found described in the literature, they propose to recognise the existence of certain forms of epileptic attacks of a reflex conditioned origin, which would especially apply to those precipitated by an emotional factor (affect-epilepsy including musicogenic epilepsy). They think that the reflex conditioned attacks are very frequent but are often not recognised as such, because of the great number of signals which constitute in the course of ontogenesis the temporary links (direct or in chain) with the epileptogenic focus and which then become apt to precipitate attacks.

20. Electronic model of the conditioned reflex. — P. Nayrac, L. Masse and J. Dujardin (Lille).

The authors present an electronic apparatus with two switches, which stand for the specific and for the unconditioned stimulus. The reaction is represented by a cathode indicator. The functioning is obtained by the charge of a condenser without intervention of a damped oscillator.

21. Automatic device for monitoring and marking stimuli used in conditioned reflex work. — A. Rémond, N. Lesevre and A. Ripoche (Paris).

The authors here describe an apparatus that allows the automatic monitoring of different phases of a conditioned reflex, e.g., the beginning and end of two stimuli, e.g. sound and light, to take the most classical association of two stimuli. This apparatus comprises the *a priori* regulation of three intervals as follows:

(1) The interval separating the onsets of the unconditioned and of the conditioned stimulus;

(2) The duration of the stimulus; and

(3) The interval separating the ends of the 1st. and of the 2nd. stimulus. On a single tracing taken from the input of the amplifier individual marking of the onset and the end of each phase of the command of the reflex, as well as the response of the subject (reflex of Ivanov-Smolenski) becomes possible with this apparatus.

22. Electromyographic study of 12 cases of spasmodic torticollis. — F. Thiebaut, F. Isch, C. Isch-Treussard and J. Jouffroy (Strasbourg).

In twelve cases of torticollis the authors have recorded the electrical activity of the posterior cervical paravertebral muscles and of the sterno-cleido-mastoideus with needle electrodes devised by Bronck. These electromyograms were taken at rest and during voluntary flexion, extension, rotation and lateral flexion of the head. The four varieties of spasmodic torticollis were studied: that is, lateral right and left, pre- and retrocollis. The observations of previous authors (Herz, Tournay and Paillard) were confirmed. As described by these authors there was always a bilateral distribution of the abnormal activity in the muscles which were studied and it was also found that the character of this activity was sometimes continuous and sometimes rhythmical.

The disturbances of muscle activity during the movement of the head were more or less pronounced in the different tracings. In certain patients signs of extra-pyramidal involvement were found and were also studied in the muscles of the trunk and the extremities.

Three tracings could be studied at different occasions and in one patient studies were carried out before and after surgical intervention.

23. Experiments with photo-electronystagmography (PENG). — H. R. Richter (Basle).

The problem of individual calibration. The methods based on the perimeter of Foerster are not sufficiently efficient in view of the fact that the method proposed by the author is 15 to 20 times as sensitive, than the usual electro-oculographic recordings.

Thus a special arrangement of light signals at the ceiling of the Faraday cage allows to carry out calibrations of minimal ocular movements. Controls by an individual calibration before and after caloric test e.g. can be carried out without requiring any change in position of the patient. Asymmetry in sensitivity of the two photo-electric cells can easily be recognized and corrected.

With a selector, it is possible to choose deviations of 2°, 5°, 10°, 15°, 20° and 30° to the right or the left, from the point of fixation. The calibration can very easily be repeated. Lineal responses are recorded between 2° and 20°. The high sensitivity of the photoelectric arrangement is characterised by a signal of 200-250 microvolts for an angular movement of the eyes of only 2°.

24. Goggles for the recording of electro-oculograms. — V. Gabercek and A. Rémond (Paris).

A plastic frame which is worn on the face like goggles supports the grooves in each of which a pair of electrodes is mounted. The distance between the electrodes can be regulated as well as the orientation and the individual position of each groove in relation to the ocular globes. An unpaired electrode is fixed in the midline on the frame and its position can be regulated vertically. It records the potential from the nasion.

The application of the oculographic goggles can be rapidly performed and allows simultaneous recording in all directions of the potential variations going along with eye movements. The goggles are devised in order not to interfere with vision nor with the conventional methods of recording brain potentials.

25. Concerning 4 c/sec. rhythms in posterior head regions in old head injuries. — P. Nayrac and M. Beaussart (Lille).

The authors report on 5 cases in which electroencephalograms were taken 10 months and 3 years after the head injury. The study deals only with the posterior rhythms which are characterised as follows: frequency varying between 3.5 to 4.5 c/sec.; distribution of reactivity as normal alpha rhythm, appearance either continuously or in organised bursts; monorhythmic and monomorphus elements; bilaterality and synchronism. These rhythms are never sinusoidal but always asymmetrical in relation to the iso-electric line. The envelope of the bursts never assumes the form of a spindle.

No relationship could be established between the type of head injury (severe or benign) and objective neurological signs on one hand and the degree of development of 4 c/sec. rhythms in posterior head regions on the other hand. It was particularly noticed that the most spectacular 4 c/sec. rhythms in which this activity was prominent was recorded from a rather large area extending forward from the occipital region in a patient who had suffered a relatively minor head injury. The only symptoms which are common to all these patients were those of a subjective complaint of the usual character. There were no signs suggesting hypothalamic lesions.

As Gastaut *et al.* have pointed out, the comparisons with other slow activities in posterior head regions as e.g. those observed in tuberculous meningitis and those sometimes observed between the bursts of spike and wave discharge in "petit mal" show that:

(1) In the first case there is a certain similarity with the records correlated with lesions of the base of the brain, but not with the typical pattern of sinusoidal monorhythmia of a slow form and posterior distribution, as described by the Montpellier school, in which the rhythms are essentially slower and more sinusoidal and are the expression of a mechanical and progressive process (hypertention of the C.S.F. in the 3rd. ventricle or basal arachnoiditis).

(2) In the second case there is a similarity only when the activity is slow and not very high in amplitude and does not appear in paroxysmal bursts.

Similar slow activities were observed in other cases, one of them was a functional dysphonia and van Reeth reported one in 1952 in a psycho-neurotic patient, in which the neurological examination was negative.

In conclusion, one may say that these electrographic patterns are rarely observed in old head injuries and the pattern and its clinical accompanying symptoms suggest that it is related to disturbances in centrencephalic and diencephalic mechanisms. These disturbances are more likely to be the expression of a dysfunction rather than of a lesion and do not seem to show any tendency to progression.

A long range study of the evolution of reactivity of this pattern is being undertaken by the authors.

26. Electrographic study of head injuries in children. — A. Lérique-Koechlin and N. Teyssonnière de Gramont (Paris).

651 tracings in 274 children were studied: 165 EEG were taken in children less than 15 days after the trauma and 67 patients were followed during 1-6 years; 50 per cent of the initial tracings were normal. The abnormal EEG presented slow waves which were often localized in temporal, parietal or occipital regions. In 76 cases this was homolateral and in 21 cases contralateral to the impact of the injury. In 44 abnormal electroencephalograms of patients without fracture, it was possible to correlate the electrographic with the clinical signs and to make the diagnosis of hematoma in 10 instances. The age of the child (2 months to 15 years) did not bear any relationship with the severity of the EEG changes, but the severity of the traumatism and the severity of the loss of consciousness, hemiplegias and convulsive seizures, when they render more serious the clinical prognosis, are accompanied by more important alterations of the EEG tracing.

Two out of 19 patients recovered without sequelae after one year, but only 58 of the 133 abnormal EEG's became completely normal again and only very slowly so. Slow waves and theta rhythms persisted very often. In 13 cases localized or generalized spike-and-wave complexes were recorded, 6 times without clinical epilepsy. In 15 cases intermittent photic stimulation became effective in producing abnormal activity. The reaction to hyperventilation very often remained very marked.

In summary, it is very important to follow up for long periods the EEG records of children who have suffered head injuries. There is a possibility of late epilepsy. The EEG is very valuable in localizing an extradural hematoma. It is also a very important prognostic aid in light head injuries.

27. Electroencephalographic study of hypothalamic amenorrhea. — F. Rohmer, R. Gandar, A. Wackenheim and A. Hollaender (Strasbourg).

EEG studies of hypothalamic amenorrhea were carried out in 26 cases and showed that in 14 cases, that is, in a rather high proportion, there were pathological alterations of the electroencephalogram. The recorded abnormalities in these 14 cases allowed to recognize the diencephalic dysfunction in 11 cases (4 times atypical spike and wave discharges and 7 times alterations of the modulation of the type seen in disturbances of arousal mechanisms). These find-

ings and the high proportion of abnormal records are very interesting from the practical point of view and justify including the EEG as a complementary examination among the methods of investigations to be used in cases of hypothalamic amenorrhea.

From the theoretical point of view it is interesting to note that EEG studies of hypothalamic amenorrheas showed that in cases with electrographic signs, as they are typical for diencephalic disturbances, there was always correlation with atrophy of the endometrium. The inverse relationship, however, did not exist. These EEG data would confirm the hypothesis of Reifenstein, without excluding the possibility of a hypothalamic origin of certain amenorrheas with hyperplasia of the endometrium.

The association of hypothalamic amenorrhea with obesity was found in 6 out of the 26 cases presented. These 6 cases showed a disturbance in regulation of the alpha activity.

In 1 case continuous theta activity was found, which was similar to that which the authors have described in cases of Babinski-Froehlich syndrome or in Lawrence-Moon-Biedl syndrome and is also similar to that recently reported by Hughes and Summers to occur in the syndrome of Sheehan.

28. Electroencephalographic studies in Grave's disease. — M. Milco, E. Brosteano, Al. Nicolesco-Catargi and B. Ionesco (Bucarest).

The authors studied 23 cases of Grave's disease which were hospitalized. Thirty-seven EEG's were taken on these patients. Abnormal tracings were found in 26 out of the 37 recordings. The alpha rhythm was either dominant or associated with other rhythms in 34 out of 37 recordings. In 33 tracings it was found that a rapid rhythm, ranging from 14 to 26 c/sec. was either predominant or associated with other rhythms. This rhythm of small or moderately high amplitude was diffuse in 28 recordings. Theta rhythms were found in 26 recordings and were most marked in anterior head regions. In 12 records bilaterally synchronous discharges of an epileptogenic type were found.

With intermittent photic stimulation there was driving, especially with slow frequencies. In 2 cases of Grave's disease the intravenous administration of Largactil produced a regularisation of the electroencephalogram, together with diminution of theta activity and of paroxysmal discharges.

The administration of Lugol solution did not modify the resting records but, after this treatment was performed for 12 days, it produced the appearance of a great sensitivity to hyperventilation.

The intravenous injection of Thyroxin produced an acceleration of the alpha frequency, an increase in the amount of rapid activities, the appearance or increase of theta rhythms and the disappearance of paroxysmal discharges.

The authors discuss the origin and possible significance of these EEG alterations.

29. A contribution to the study of arterial hypertension. — O. Sager, E. Brosteano, V. Stanesco, M. Moisano (Bucarest).

In 61 patients suffering from essential arterial hypertension the EEG, the clinical symptomatology and the hemodynamic adaptation to effort was studied. The following conclusions were reached:

1. The EEG abnormalities can be divided into 2 groups:

(*a*) the first consists of abnormalities of an excitatory type with rapid background activity of a diffuse distribution and spike discharges and local rapid activity of great amplitude. These latter disturbances were found in 3 patients who died soon afterwards;

(*b*) the second group consists of an inhibitory type of activity, with slow waves on a normal background rhythm or a slow and diffuse dysrhythmia.

In some cases the authors found paroxysmal discharges of an epileptic character.

2. In the cases which were studied there was no correlation between the EEG changes and the changes observed in the fundus.

3. When the hemodynamic adaptation to effort was deficient, the EEG was always altered.

4. The patients suffering from this disease for more than 4 years showed mostly an EEG pattern of the excitatory type.

5. The oscillating form of arterial hypertension was most often associated with an excitatory type of EEG, with diffuse rapid activity.

The authors insist on the importance of using several methods of investigation to establish a clinical prognosis.

30. Two cases of post-traumatic extradural hematoma in children. Similarities and particularities of their EEG tracing. — J. Lebascle, A. Massebœuf and R. Acquaviva (Casablanca).

The post-traumatic extradural hematoma is usually considered as rare in children. The authors report two recent observations which showed similar clinical and EEG manifestations:

(1) A coma of variable degree, accompanied by modifications of the cardiac rhythm.

(2) An EEG tracing reminiscent of that seen during sleep, with attenuation or disappearance of rapid activities and of the slow, diffuse paroxysmal changes on the side of the lesion. After operation these tracings became rapidly normal again.

The authors discuss some hypotheses concerning the origin of these electrographic manifestations.

31. Electrographic and clinical correlations in 802 head injuries. — R. and C. Rabache, E. W. Fünfgeld and H. Gastaut (Marburg/Lahn, Marseille).

In 802 cases of head injuries, having occurred mostly in young or middle-aged adults most of whom were examined between the first and sixth month after the trauma, or 2 or 3 years after, the following observations were made:

(1) Almost half of the cases had perfectly normal electroencephalograms;

(2) One tenth of the cases showed desynchronized tracings and another tenth tracings with bilateral slow waves. Almost one tenth of the records was characterized by an alpha rhythm of a frequency of about 13 c/sec. or by a rapid dysrhythmia of a generalized distribution.

(3) Almost one-fifth of the cases showed an electrographic focus (4/7 of the cases of an irritative character and 3/7 of a non-irritative character), localized in the temporal region in 5/6 of the cases (left temporal region in 2/3 of these cases, right temporal region or bilateral temporal abnormalities in the remaining third).

Since it is logical to include the rapid alpha rhythm and certain tracings with desynchronized ac-

tivity among the normal electroencephalographs, one can conclude that 40 per cent only of the head injury cases have abnormal electrograms which may be divided into 2 categories of equal importance:

(1) The slow and rapid dysrhythmias and certain desynchronized electrograms, dysrhythmias which are dependent upon alterations of subcortical structures regulating cerebral electrogenesis (commotio cerebri affecting the brainstem).

(2) Focal abnormalities related to an area of contusion most often localized at the site of contrecoup (lesion of the tip of the temporal lobe and of the para-rhinal area against the sharp edge of the lesser wing of the sphenoid and against the free edge of the tentorium).

Among these abnormalities, those of a localised character are more significant. It is among those cases that one finds the highest incidence of post-traumatic neurological signs and post-traumatic epilepsy.

32. EEG studies in frontal syndrome due to tumors: an electrographic and clinical study of 60 cases of frontal and fronto-temporal tumors. — M. B. Dell (Paris).

The material here presented is studied in relation to different mental disturbances which constitute the frontal syndrome as seen in tumors. The anatomical and histological characteristics of the lesion do not explain the whole electrographic picture. Certain aspects especially the modification of the background rhythm and of its reactivity, but also the extent of the slow wave disturbances, can be correlated with the presence and importance of observed mental disturbances.

These are schematically divided into three groups:

(*a*) personality disturbances, involving especially affect and behaviour;

(*b*) disturbances of attention; and

(*c*) confusion.

The extent of the abnormalities due to lesions represented by polymorphous delta activity depends upon the aspect of the background activity upon which it is superimposed. The study of these EEG changes allows to establish a regular progression of electrographic signs starting with a normal tracing and leading to a diffusely disturbed electrogram with bilateral delta activity of a diffuse character. This progression is not a direct relationship with the size of the tumor, but goes parallel with the increasing severity of the psychiatric symptomatology. The minimal abnormalities which are well localized when they are present are superimposed upon a background activity which in general appears to be quite normal. This is found in cases where mental disturbances are absent or only involve personality changes, whereas consciousness in the restricted sense is not affected. On the other hand, the extension of the abnormalities as characterized by a deterioration, or even complete disappearance of physiological background rhythms, accompanied by global and important disturbances of the reactivity, is found in cases with massive mental disturbances affecting the function of consciousness.

33. The electroencephalogram in 37 cases of intracranial meningiomas. — R. Rouvray and A. Rémond (Paris).

The electroencephalogram in 37 patients with intracranial meningiomas, which were verified surgically and anatomically, was studied. It was thus possible to give evidence for a certain number of characteristic changes which were common to electroencephalograms corresponding to meningiomas of the same localization, and to indicate in what proportion the electroencephalogram allowed in this series to lateralize and localize the lesion. Moreover, the evolution of preoperative and post-operative records could be studied in a certain number of these patients.

34. The evolution of the EEG changes following psycho-surgical operations. — J. Gaches and M. Dondey (Paris).

Parallel with a psychiatric study, 36 non-epileptic patients (either mentally ill or suffering from intractable pain) which were treated by pre-frontal psycho-surgical procedures, were followed up from the EEG point of view over a period of more than 5 years. Nineteen among these patients could be subjected to a control EEG examination. Only one out of 36 cases were epileptogenic sequelae observed. However, in 7 cases the EEG showed paroxysmal abnormalities, either of a typical or atypical character, without clinical manifestations.

The residual post-operative EEG abnormalities disappeared in 12 cases after a period of not less than 6 months but of variable duration. Paroxysmal abnormalities usually appeared after an interval of 24 to 30 months period.

35. The influence of experimental epilepsy produced by cortical stimulation upon responses of the specific and unspecific systems to auditory signals. — M. Jouvet, O. Benoit and J. Courjon (Lyon).

Experiments were carried out on curarized or "encéphale isolé" cats. The responses recorded in auditory relay stations (cochlear nucleus and medial geniculate body), in unspecific structures (reticular formation) and on the auditory cortex, were studied after faradic stimulation of different cortical regions carried out at variable intensities.

The stimulation of a limited area of cortex (sensorimotor, auditory I and II) produces an inhibition of the auditory signals at the level of the first auditory relay station, i.e., in the cochlear nucleus. This fact is interpreted as evidence for the existence of corticofugal inhibitory fibers. A depression of the auditory responses in the medial geniculate body was also observed after stimulation of a wider cortical area. At the level of auditory area I, several phenomena can be observed:

(i) inhibition of rapid and slow responses;

(ii) inhibition of the slow response followed by a facilitation of the response with a slow afterdischarge.

In certain cases it was possible to obtain a persistent inhibition of the response in the reticular formation, while the responses in the specific systems had already become normal again.

The significance of these observations is discussed in relation to the question of cortical projections to centrally located multisynaptic formations and in relation to disturbances of consciousness observed in certain epileptic states.

36. The electrical activity of the hippocampus of the cat during an experimentally produced convulsive seizure. — A. Kreindler, V. Voiculesco, R. Brosteanu and I. Voinesco (Bucarest).

During a convulsive seizure precipitated by electroshock one finds in all cortical and subcortical derivations an electrical activity which is nearly synchronous. Only the record from the hippocampus forms an exception to this rule, since it seems to be made up of an association of several rhythms:

(*a*) A perfectly regular rhythm of 12-14 c/sec. which is seen to usher in the hippocampal seizure and which resembles that recorded from other areas, but whereas the rhythm in areas outside the hippocampus rapidly slows down to 2-3 c/sec., the frequency of the hippocampal rhythm slows down only slowly to about 10 c/sec. At this time each wave constituting the rhythm, doubles up.

(*b*) A rapid rhythm of 20 c/sec. regular in form and entirely comparable to the ''comb'' shaped rhythm which the authors described in mesencephalic and diencephalic formations. It is highly probable that this rhythm, which appears toward the end of an epileptic attack in the diencephalic and mesencephalic formations is of hippocampal origin.

(*c*) The rapid hippocampal rhythms are modulated by slow synchronous waves appearing in all derivations and which are particularly manifest during the clonic phase.

(*d*) The presence of numerous spikes with an amplitude in excess of 1 mV. seems to be characteristic for the activity of the hippocampus.

The particular pattern of the hippocampal rhythms suggests the existence of a special hippocampal circuit which functions during the convulsive attack.

37. One hundred and seventeen cases of paroxysmal bilaterally synchronous EEG changes; an analysis of electrical and clinical varieties of this rhythm, its course in time and therapeutic results. — E. Meurice (Liège).

Among all the epileptic cases which were examined in the EEG laboratory of Liège the author selected all the electrograms presenting primary bilateral synchronous paroxysmal discharges: typical electrographic petit mal, atypical petit mal, myoclonic epilepsies, unspecific centrencephalic epilepsies. Two hundred and eighty-four records were thus studied which were taken of 117 patients, among which 69 were examined several times (in half of these patients the observation period extended to two years). The treatment given to these patients was suggested to the treating physician by the medical personnel of the laboratory.

The electroencephalographic pattern of typical petit mal (not associated with multiple spikes) is characterized clinically by ''absences'' or by attacks without aura or by an association of both. The initial loss of consciousness can be considered as the ''aura'' of purely centrencephalic attacks.

Atypical petit mal was characterized by clinical symptoms of a more varied character.

Myoclonic patterns and atypical centrencephalic patterns are only rarely associated with ''absences'' but with a great variety of attacks, among which many resemble closely the pattern of temporal lobe seizures. Only among these two groups was true photosensitivity encountered. Among 28 patients which were sensitive to photic stimulation, only 4 had paroxysmal discharges with photic stimulation only.

In general the treatment with Diones (3 capsules a day on an average) plus 1 tablet of Epipropane was able to diminish the attacks in 65 per cent of the cases. When this treatment was without effect the dosage was usually not sufficiently high. Adding hydantoines often improved the ''temporal'' component very markedly, which was found to be associated with the clinical and electroencephalographic picture in certain cases.

In some of the records there was a change of the pattern during the time of observation. This consisted either in a transition from a bilaterally synchronous paroxysmal pattern to another which was more atypical or the electroencephalogram showed more, or in other cases less, evidence of a focal component. In a single case there was also a correlated change in the clinical pattern. Most of the patients seen were children. They greatly benefited by a treatment which was adapted to their individual needs.

38. Correlations of electrographic and clinical symptoms in 150 cases of nocturnal attacks. — M. Tinant (Namur).

One hundred and fifty patients were studied in which the clinical paroxysmal manifestations were only nocturnal, consisting either in epileptic attacks, episodes of sleep walking, or nightmares. A few cases of narcolepsy were also studied.

A general analysis of these cases showed that this group as a whole shows very little difference when compared with a control group of epileptics having diurnal attacks.

Anti-convulsant treatment of the usual nature is sufficient to cure the attacks and to improve the electrogram. Treatment with ''psychamines'' was necessary in patients with a normal spontaneous electrogram and with paroxysmal discharges of sharp theta waves appearing during the early stage of natural or drug-induced sleep and in several cases with nightmares.

In patients above the age of 50 with nocturnal attacks having appeared late in life, a treatment as applied to vascular disease is usually more efficient.

39. Considerations concerning electroencephalograms in 200 cases of generalized epileptic seizures which started late in life. — H. Giroire, A. Charbonnel, P. Vercelletto and Trichet (Nantes).

Two hundred patients with generalized epileptic attacks which had started late in life were studied. If one excludes the cases where the attacks are only part of a general symptomatology of a known clinical syndrome or those which can be explained on the basis of known pathological lesions antedating the onset of the attack, the following observations can be made :

(1) In the region where the authors studied these cases chronic alcoholism was the most frequent etiological factor. The EEG in this group was normal in 3/4 of the cases.

(2) In the group of cases where epilepsy was the only symptom when the first examination was taken, the suspicion of a tumor was always very strong. EEG alterations such as polymorphous delta activity, which could have pointed in this direction, were however rare. On the other hand, the possibility of brain tumour cannot be ruled out by any electrographic pattern.

(3) In cases with centrencephalic type of discharge the possibility of a late onset of idiopathic epilepsy cannot be excluded.

One observation is discussed where the similarity of the electrographic pattern seen in the patient and in a close relative of his constituted a very important argument in favor of this hypothesis.

40. Interparoxysmal phenomena in cases with bilaterally synchronous spike-and-wave discharges. — P. DE CASTRO, J. M. SACRISTAN, G. MOYA and F. R. SANABRA (Madrid).

The authors studied the interparoxysmal EEG phenomena in 100 epileptics whose tracings were characterised by bilaterally synchronous spike-and-wave discharges of varied morphology.

(1) In 50 per cent of the cases there was diffuse dysrhythmia of variable intensity. The degree of this disturbance seemed to be correlated with the irregularity of the spike-and-wave complexes seen during the paroxysmal episodes.

(2) The following random phenomena were observed:

(*a*) *In anterior head regions*: theta activity was observed in some cases or bursts of slow waves and of spike-and-wave complexes restricted to one or two single discharges and strictly localized to the frontal regions. These complexes were either slower or more rapid than the spike-and-wave discharges of the more characteristic pattern seen in these records. All the patients who showed this type of tracing suffered from grand mal.

(*b*) *In posterior head regions*: trains of regular slow waves at 2-3 c/sec. were seen in some cases, and these were often accompanied by a spike in one or the other of the temporo-occipital regions. This was often bilateral and would disappear with eyes opening and during intermittent photic stimulation. This pattern often preceded the discharge of the typical bilaterally synchronous spike-and-wave complexes which sometimes did not appear in a sudden way but seemed to develop out of this slow wave pattern.

The authors are of the opinion that in centrencephalic epilepsy, in addition to the disturbances originating in the diffuse thalamic projection system, as characterized by bilaterally synchronous spike-and-wave discharges, there is often a participation of the specific thalamic nuclei which would find expression in the interparoxysmal phenomena discussed in this study.

41. A report on certain spontaneous or Pentothal-induced manifestations and on the neuronal systems which control these discharges. — J. SCHNEIDER and J. J. BLUM (Colmar).

The authors discussed the following electrographic manifestations:

(1) Rapid activity of 25-30 c/sec. appearing in bilaterally synchronous waxing and waning bursts in anterior head regions. From clinical and neurophysiological observations it is probable that the mesencephalic reticular formation and the corticopetal systems are involved in the genesis and propagation of these activities.

(2) Slow waves of a frequency of 2-3 c/sec. appearing in high amplitude bilaterally synchronous bursts in anterior head regions. The clinical symptoms in these patients were discussed. The anatomical and physiological characteristics of the systems involved in this abnormality were reviewed.

(3) K-complexes were produced by pharmacological means. Clinical and neurophysiological aspects of this phenomena were discussed, as well as the neuronal systems capable of playing a role in the genesis and propagation of these electrographic disturbances.

42. The electroencephalographic changes in sleep produced by steroid compounds with anaesthetic properties: sodium succinate of 21 hydroxy-pregnandione (Viadril). — R. DAMASIO and V. GIRARD (Paris).

This steroid compound is characterized by hypnogenic and anaesthetic properties. Sleep can be obtained with a fairly stable dose of 1.50 gm. and the awakening from sleep is similar to that from natural sleep.

The successive EEG changes resemble those which are induced by Pentothal but the depression of somato-vegetative mechanisms remains more discrete.

Four electrographic and clinical stages, which are correlated with each other can be distinguished and the transition from one stage to the other is gradual:

(1) The stage of sleep induction: slight slowing of the mental processes accompanied by rapid rhythm predominating in anterior head regions;

(2) Stage of transition to sleep: appearance of rhythmical bursts of high amplitude and sharp theta waves;

(3) Stage of light sleep evolving toward deep sleep: augmentation of the amount of slow waves and progressive increase of their amplitude and duration;

(4) Stage of very deep sleep or anaesthesia: this stage is marked by the appearance of silent intervals of a duration of one to several seconds, which are separafed by rhythmical bursts of a spontaneous onset.

The arousal reaction persists during the first stage, becomes slightly obtused during the second stage and progressively disappears during the third stage.

In view of the complexity of the mechanisms regulating alertness and sleep only hypotheses can be formulated concerning the mode and locus of action of this drug. It is probable that this steroid acts by humoral factors upon oxydative processes and it was attempted to verify this by studying the effect of cytochrome injections upon arousal. In accord with recent findings one can consider as probable that this drug acts mainly upon the unspecific reticular formation controlling the different levels of alertness. The practical use of the compound is summarily reviewed.

43. Studies with a new activating agent for the electroencephalogram: "Bemegride" ("Megimide" or "NP13"). — R. COIRAULT, R. DAMASIO, E. SCHULLER, V. GIRARD and H. FARAND (Paris).

Isolated as a separate compound by Shaw in 1954, ''Bemegride'', was used as an antagonist to barbiturates. In view of its stimulating effect upon the nervous system, it was felt that it would be of interest to study its effect upon the EEG with the method of Delay and his collaborators consisting of administering progressively larger doses of this compound. This report deals with the first observation which were made upon a still limited number of cases. This compound appeared to be an excellent activator of the electroencephalogram. This drug is particularly interesting in view of the fact that it is better tolerated than Cardiazol. Its action is also more gentle and the conditions in which it can be used seem to be more numerous. Moreover, this compound

is rapidly eliminated and barbiturates (specially pentobarbital) represent a powerful antidote with immediate action when injected intravenously.

Finally, Bemegride is of interest not only from the neurophysiological point of view but also from the clinical point of view, since studies of the intensity and duration of its action suggest that it produces a nervous hyperexcitability and that therefore its use in different neurological syndromes may well be justified.

44. Technique of activation of the electroencephalogram by NP13 or Megimide. — G. and J. Verdeaux, G. Drossopoulo, P. Chanoit and E. Schuller (Paris).

The authors describe the technique which is used at the present time for activating the EEG with the imide of the ethyl-methyl-glutaric acid, a compound used to replace penta-methylenetetrazol (Metrazol).

The authors cite the complete bibliography concerning this new compound.

45. Modifications of cerebral electrogenesis produced by non-convulsive doses of Cardiazol. Quantitative relationships between doses and effects. — Z. Drohocki and L. Goldstein (Paris).

The introduction of quantitative methods in electroencephalography by the application of integration of the variations in amplitude (integrator of Drohocki) permits the study of the pharmacology of the cerebrum and to establish quantitative relationships between doses and effects.

The experimental procedure was standardized. The electrical activity during wakefulness was first recorded. On the basis of the frequency of the integrals of electrogenesis, the mean value was calculated and the limits of significance were established. The drug to be studied was then injected and the period of its action divided into a certain number of intervals of equal duration, during which the mean electrogenesis was calculated. It is sufficient to compare the value thus obtained with those characteristic for the variations of the mean during wakefulness in order to deduce immediately if there is significant or non-significant variation.

The authors studied the action of small doses of Cardiazol with this method. Intravenous injection of 2.5 mg. in rabbit was followed by a significant decrease of the electrogenesis, which lasted for about 200 sec. After an injection of 5 mg. the events were characterized by an initial decrease, which was followed by an augmentation of the electrogenesis. But in this situation the period of decrease in electrogenesis was shorter in duration. The injection of 10 mg. produced a considerable augmentation of the electrical activity for a period of 1,400 sec. which was preceded, however, by a period of decrease lasting for 80 sec.

It results from this study that Cardiazol in small doses produces a decrease in electrogenesis, a decrease which probably corresponds to an inhibitory process.

46. Modifications of the cerebral electrogenesis under the influence of curare. — Z. Drohocki and L. Goldstein (Paris).

The quantitative methods used in the analysis of the effect of Cardiazol also allowed to study the problem of the action of curare upon the central nervous system. The question under study was whether the possible effect upon the electrogenesis is independent or not from that exerted upon respiration. The authors recorded in the rabbit simultaneously the electroencephalogram and its integral, as well as respiration, whose integral was calculated by direct planimetric methods.

This study shows that small doses of curare (100/kg.) which did not necessitate the use of artificial respiration and did not produce any sign of suffocation, produced inverse modifications of respiration and electrogenesis. While respiration was diminished by 30 per cent, electrogenesis was augmented by 15 per cent. Therefore, to the contrary of what is usually believed, small doses of curare augment the electrogenesis by a mechanism which is distinct from that exerted upon respiration.

In view of the fact that the modifications of electrogenesis seem to depend upon the action of curare directly, it was attempted to study this mechanism more closely by statistical methods. Histograms of distribution of frequencies of amplitudes showed that, while in the awakened state electrogenesis is concentrated and grouped around a single value, which is a phenomenon dependent upon the action of regulatory mechanisms, under curare a less pronounced concentration is noted and there is a broadening of the zone of maximum. These modifications are the expression of a dysfunction of the regulatory system.

BOOK REVIEWS

Edited by CHARLES E. HENRY

CLINICAL ELECTROMYOGRAPHY

T. TOKIZANE and N. TSUYAMA

Kyodo Isho Publishing Co., Tokyo, 1955, about $2.00

This Japanese text book of clinical electromyography was first published in 1952. It fulfilled the growing need for general information in a field which paralleled the progress of modern neurology.

A comprehensive monograph, it was written by two authors, one a physiologist, the other an orthopedic surgeon. The purpose was to cover the subject as broadly as possible, including both the clinical and the physiological aspects. To the unusually abundant number of plates (174) and rich bibliography of the first edition were added the most recent advances in a second printing in 1955. In chapter I, devoted to the Neuromuscular Unit, the authors describe two types of motor units in the peripheral neuromuscular system: a tonic unit concerned with postural adjustment, and a kinetic unit related to phasic movement. Anatomically, the tonic motor unit is the main component of red muscle, being innervated by small anterior horn cells with thin fibers, whereas the kinetic motor unit is related to pale muscle and innervated by large motoneurones with thick fibers.

In chapter II, the Method of EMG Examination, the construction and use of different electrode models (surface, concentric and monopolar) as well as amplifying and recording devices are amply and adequately described. The people concerned with clinical EMG will especially appreciate the extensive discussion of artifacts and other possible sources of error which might arise during examination.

Chapter III is on the Functional Activity of the Normal Motor Unit. Firstly, the authors describe the difference in wave form as derived by various types of electrodes. The different figures noted by individual workers for the duration of spike discharge when led off by needle electrodes are also analyzed. It is emphasized that the spike duration as well as the wave shape and its amplitude vary according to several factors; namely, the architectonics of muscle fibers in a single unit, the size of the active electrode, and the distance between the active electrode and the active unit being recorded.

The study of fluctuation of discharge interval is the main topic of this chapter and one which the authors insist upon throughout the entire monograph. This original Japanese observation has not been taken up by most European and American workers. As studied by drawing of fluctuation intervals, correlograms and standard deviation-average interval curves, several types are described, one of them being apparently synchronized with respiration. These fluctuations appear to be the manifestation of the excitatory or inhibitory state of anterior horn cells. They are modulated by proprioceptive impulses and excitatory or inhibitory processes of the cerebral cortex as well as other regulatory mechanisms from the cerebellum and brain stem. As investigated from the study of fluctuation of discharge interval, there are remarkable differences between the kinetic and tonic motor units, there being a larger standard deviation for the kinetic motor unit than for the tonic one, the average interval being the same. Furthermore, muscles concerned with fine movements e.g. in face and finger, show a larger standard deviation than those related to coarse movement.

It is suggested these observations could be related to the extent of motor representation on the cortex as illustrated by the homunculus of Penfield and collaborators. This is borne out by the fact that a muscle occupying a large area in the motor cortex shows a larger standard deviation. The present reviewer would agree with this point of view following his experience based upon the findings of EMG studies in patients having undergone motor and premotor removals.

Chapter IV is entitled Functional Activity of the Abnormal Motor Unit. Here is presented a lucid and clear classification of abnormal patterns. At the present time, the most confusing subject of clinical EMG is pattern terminology, as related to etiology, especially complex polyphasic potentials. These are classified into four patterns interrelating both wave form and etiology: (1) complex motor unit potentials (2) reinnervation potentials (3) synchronization (complete and incomplete) potentials and (4) grouping potentials.

The complex motor unit potential, being up to 1.5 mV. in amplitude and from 5 to 20 msec. in duration, is similar to the nascent motor unit (Weddel *et al.*) or recovery potential (Sargent). It is observed in the course of progressive reinnervation or denervation.

The reinnervation potential, which has an amplitude of up to 15 mV. and of 5 to 10 msec. in duration, appears at least one month following the onset of nerve regeneration. It is caused by a motor unit having a much larger innervation ratio as compared

to its territory of distribution before injury; thus one nerve fiber controls an additional group of muscle fibers as well as its own, whereas the complex motor unit potential would only be concerned with its proper fiber group.

Synchronization and grouping potentials are differentiated as follows; while the needle electrode is in a fixed position, individual waves in a train of synchronization potentials are very similar to one another; on the contrary, grouping potentials display a unitary difference as well as additional unit spikes with the use of a thin needle electrode. These individual spikes never appear with synchronization potentials which are associated, pathologically, with anterior horn cell disorders.

Two theories have been advanced to explain fasciculation: one holds that it is due to hyperirritability of the anterior horn cells, the other that hyperirritability exists in both muscle fibers and end-plates. The authors recognize the existence of these factors and differentiate them on the basis of wave form. Hyperirritability of the anterior horn cell is evidenced by simple fasciculation and incomplete as well as complete synchronization patterns, whereas hyperirritability of muscle fibers and motor end-plates shows simple fasciculation and complex motor unit patterns. In theory, this classification would appear logical as regards etiology, but in actual practice the various differences in wave form are difficult to differentiate.

Chapter V describes the Practice of EMG Examination. There are excellent pictures and tables illustrating anatomy, innervation (spinal and peripheral) and the function of individual muscles. It is emphasized that the EMG should be recorded under various conditions; at rest, during voluntary contraction as well as passive stretch and electrical stimulation of the related nerves. In addition, the authors suggest the examination be done with the purpose of studying the interval diagram of a single unit as altered by reflex testing. This method is so sensitive as to reveal the existence of a latent Babinski in normal man while studying the extensor hallucis. This is evidenced by the shortening of the firing interval when the sole of the foot is stroked in the usual manner.

Chapter VI is devoted to Diagnosis by EMG. The various entities are discussed: myopathy, disorders of neuromuscular transmission, peripheral nerve diseases, cord lesions and upper motor neurone diseases. The authors insist on the advantages of EMG in upper motor neurone disorders. It has been found that, notwithstanding the degree of rigidity in cerebral palsy, the discharge frequency of a single motor unit is constant, at about 8 to 10 per second. In other words, the number of motor units involved and not the frequency of discharge determines the degree of rigidity. Cerebral palsy itself, according to EMG, is classified into several types: (1) hypertonic-hypokinetic, (2) hypotonic-hyperkinetic, (3) hypertonic-hyperkinetic, (4) normotonic-hyperkinetic.

Chapter VII is on Prognosis in EMG, discussing mainly, peripheral nerve injuries, poliomyelitis and other spinal cord disorders. Chapter VIII discusses the role of EMG as regards the indications and results of various therapeutic agents. In the final chapter, the authors review briefly various pathophysiologic mechanisms and their role in the different peripheral and central nervous system disorders. There is also included an outline of several problems requiring further investigation.

On the whole, the book is an excellent treatise of this subject in Japanese. It is well worth translation into English and should become a classic in electromyography unexcelled in English literature.

MITSUO NUMOTO, M.D.

ELECTROCHEMISTRY IN BIOLOGY AND MEDICINE

Edited by THEODORE SHEDLOWSKY

(Sponsored by The Electrochemical Society, Inc. New York)

New York, John Wiley & Sons, 1955, 369 pp., $10.50

This book contains a number of reviews of fundamental concepts underlying bioelectrical phenomena. Its range and spirit are set by an introductory paragraph of Dr. Shedlovsky in which he writes:

> "Electrochemistry is concerned with the electrical properties and behavior of substances and with the transformation of chemical energy into electrical energy or vice versa. It is related to biology and medicine in two ways. First it provides powerful laboratory methods and tools for the study of biologically important substances, such as viruses, hormones, enzymes and other proteins, and also for the determination in biological environments of such factors as acidity, oxidation-reduction, ionic mobility, activity and diffusion, dielectric constant and dipole moments. Second, living organisms and in fact all living cells are complicated electrochemical systems capable of transforming chemical energy and ionic transport into electrical signals. With appropriate appara-

> tus the neurophysiologist may examine such electrical signals to learn what he can about the functions of nerve and muscle. The medical clinician, armed with a substantial background of correlated, empirical knowledge, observes the electrical signals from the heart or from the brain and thus is aided in arriving at a diagnosis.''

The volume covers a wide variety of topics in 19 contributions from 23 authors, beginning with a paper by Hitchcock on membrane potentials due to the Donnan equilibrium and ending with one by Jasper on the electrical signs of epileptic discharge. Of especial interest to neurophysiologists is Cole's review of ions and potentials, in relation to the nature of the nerve impulse and Grundfest's paper on the electrochemical potentials of bioelectric tissues. Cole discusses current explanations of the propagation of the nerve impulse and reviews his own experiments with Curtis and the classic work of Hodgkin and Huxley on squid nerve. While the roles of sodium and potassium in relation to the resting potentials and action currents of nerve have been greatly clarified by work reviewed by these authors, the mechanisms controlling ion flow and the ultimate nature of the reexchange of the ions after passage of the action current is not yet satisfactorily understood. Grundfest's paper especially points out controversial aspects of the problems involved and criticizes the role of the Donnan equilibrium in accounting for the resting potentials. He presents ingenious experiments with axons and electroplaques of the electric eel to shed light on aspects of the controversy.

These papers are followed by one by Nachmansohn and Wilson on dynamic structural aspects of membranes involved in the generation of bioelectric potentials. These authors consider among other things the role of acetylcholine as a regulator of membrane structure that in turn controls the ionic movements responsible for the measured potentials.

This reviewer has been impressed for many years by what the plant physiologist has contributed to neurophysiology in his studies of the greatly slowed and readily analyzable bioelectric phenomena of large plant cells such as *Valonia, Nitella,* and *Halycystis.* More than a quarter of a century ago Osterhout described diffusion potentials primarily due to potassium, across the protoplasmic membranes between vacuolar sap and fluid environment. These cells' resting potentials and action potentials, including after potentials, bear many points of resemblance on the slow time scale of the plant cells to those of nerve. The dynamic steady state resulting from metabolism (only dead cells are in thermodynamic equilibrium) has been elucidated in these cells by Osterhout and his students. Two excellent papers, one by Blinks on electrical properties of large plant cells and another by Osterhout on the apparent violations of the all-or-none law in relation to potassium in the protoplasm discuss electrical properties of the plant cells in terms of macroscopically analyzable metabolic and ionic events occurring across heterogeneous protoplasmic membranes of the cells.

Following the first paper by Hitchcock there are papers by Scatchard on the transport of ions across charged membranes; a paper by Solner on the electrochemistry of porous membranes and one by Solner, Dray, Grim and Veihof on membranes of high electrochemical activity of biological interest. Solner's discussion of anomalous osmosis and of the properties and preparation of membranes that produce it together with accompanying bioelectrical effects is especially illuminating. Other papers of fundamental significance are those of Otto Schmidt on dynamic negative admittance components of statistically stable membranes and of Longworthy on diffusions in liquids and the Stokes Einstein relation.

Two papers, one by Tanford and the other by Carr, deal respectively with ion titration curves of proteins and with ionic activities in protein solutions. A paper by Müller considers polarographic behavior of various plasma proteins, and one by Snell deals with activity coefficients of sodium and potassium phosphates in aqueous solutions. Some of the papers presuppose for full understanding a knowledge of physical chemistry possessed by few physiologists including this reviewer, but despite this difficulty the neurophysiologist will find the book a rewarding review of basic matters underlying the phenomena of action currents, resting potentials and their relation to metabolic events and properties of membranes.

The last three papers deal with topics closer to the professional activities of most of the readers of this Journal. Johnston and Cordes discuss electrocardiography and electrocardiographic leads; Bagchi writes on the preoperative electroencephalographic localization of brain tumors and Jasper concludes the volume with a short paper on the electrical signs of epileptic discharge.

The book grew out of a symposium of the Electrochemical Society and its contributors represent a wide range of interdisciplinary interests. It could have been improved had there been more of an exchange of views among the participants, possibly by publications of discussion from the floor or by a chapter attempting some syntheses and interrelationship of the material. Each essay is a unit by itself and the reader is left on his own in relating the significance of the wide range of contributions to his professional interests. But aside from this the volume is to be strongly recommended to those concerned with the basic underpinnings of neurophysiology.

HUDSON HOAGLAND, M.D.

CORRELATIVE NEUROSURGERY

EDGAR A. KAHN, ROBERT C. BASSETT, RICHARD C. SCHNEIDER, and ELIZABETH C. CROSBY

Charles C. Thomas, Springfield, Ill., 1955, 413 pp., 235 illus. $19.50

This represent the most complete textbook of neurological surgery as yet in print. Various phases of neurological surgery have been more definitively presented in monograph form but no single book with which I am familiar covers the entire field so well. The attempt to correlate the anatomy and physiology with the pathologic process is admirable and will certainly stimulate others to do the same.

The special chapters on electroencephalography, neuro-endocrinology and radiology are fitting and emphasize the importance of good teamwork if the neurosurgeon is to take advantage of all diagnostic aids. The chapter on electroencephalography in particular is stimulating and graphically illustrates the need for a closer liaison between the encephalographer and the surgeon. Superficially, this chapter presents a brief resume of the contribution the electroencephalographer may make to the neurosurgeon in terms of diagnosis and localization of brain tumor. On a far more sophisticated plane the authors offer valuable information of use to the encephalographer whose clinical experience with space-occupying lesions is less complete. The concept of what is an adequate electroencephalogram to exclude or localize a brain tumor is particularly well done and deserves to be read by all interested in the field, especially those working in general hospitals. Numerous hints as to reasons for false localization and even aids to localize posterior fossa lesions should augment the experience of even the most able encephalographer. Discussion of more common types of tumor both from the pathological viewpoint as well as the anatomic location with these respective electroencephalographic peculiarities will serve as a reference for those faced with similar clinical problems. Only by similar technique and dedicated honesty will electroencephalography reach an equal place as a vital diagnostic tool in all neurosurgical centers. One wishes a similar chapter on anesthesia had been included.

The illustrations claim special tribute as they are unique and frequently vividly portray anatomic associations which would otherwise be obscure. The quality of the X-ray reproductions and gross anatomical specimens is excellent. They complement the text in a very real way and serve to better correlate the pathologic process with the clinical signs. This is of particular value to the young neurosurgeon whose clinical experience is limited.

The chapter on the closure of scalp defects is especially useful as this is a problem which is encountered rarely and receives little attention in many training centers. The occasion which does arise is frequently of an acute nature and does not allow a leisurely perusal of plastic surgery texts.

Omissions in a text are inevitable. No mention of sympathetic surgery or peripheral nerve surgery detracts from the book as a definitive work. Some controversial attitudes are taken and while the preface specifically notes that the contents are the ideas of the authors, occasionally one wishes more generally acceptable views were at least presented. There are minor points and should not depreciate the overall value of the book.

One senses in reading this book that it was a labor of love, that while much time and work went into it, the authors are basically proud and at times enjoyed its preparation. The low key in which ideas are presented makes the authors seem approachable and enables one to disagree with specific points with the feeling that such dissention might be well received. Perhaps this is the essence of scientific approach.

It is to be hoped that the price of this book will not prevent the wide dissemination to the young neurosurgeons which it deserves.

REMBRANDT H. DUNSMORE, M.D.

CYTOARCHITECTURE OF THE HUMAN BRAIN STEM

JERZY OLSZEWSKI and DONALD BAXTER

J. B. Lippincott Co., Philadelphia. 1954, 199 pp., $16.00

The interest in the morphology of the brain stem has been revived in recent years by physiologic studies on the reticular formation, a region which has been insufficiently investigated anatomically until now. The present atlas originated in an attempt to fill the need of a more intimate knowledge of this area and will, therefore, be highly welcomed by all trying to correlate physio-pathologic and anatomic data related to the reticular formation. The altas is based on a study of Nissl stained cross-sections through 15 human brain stems. In the first part, one finds a series of 19 semischematic representative sections of the brain stem accompanied by low-power photomicrographs, while descriptions of the individual nuclei supplemented by photomicrographs at higher magnification compose the second part. Besides portraying all known nuclear structures of the medulla oblongata, pons and midbrain, the authors have delineated several previously unknown cell groups, particularly within the reticular formation on the basis of cytoarchitectonic criteria. They attempt to subdivide the reticular formation into regions of specific cytoarchitecture and to classify all such regions as nuclei, although they recognize that the major part of the reticular formation is populated by loosely distributed cells of more than one type. The question does not seem unjustified as to which degree a subdivision of such areas is possible. For instance, in the midbrain tegmentum a nucleus cuneiformis and a nucleus subcuneiformis are differentiated; the presence of some large cells, lesser degree of cellularity and of glial satellitosis is said to distinguish the nucleus subcuneiformis from the nucleus cuneiformis. The border between these nuclei, however, is rather indistinct. Whether physiologic correlates to these rather vague morphologic differences exist, future research will have to ascertain. With its beautifully reproduced photomicrographs, this atlas will be a valuable addition on the shelves of everyone interested in the morphology of the human brain.

E. A. SPIEGEL

ERRATUM

In the August issue, page 502, fig. 2 should have been fig. 3 and fig. 3 should have been fig. 2.

INDEX TO CURRENT LITERATURE

Edited by CHARLES E. HENRY
Institute of Living, Hartford, Conn. U.S.A.

AMBROSIO, L., MAZZA, V. e SERRA, C. Comportamento della attività elettrica corticale e dell'equilibrio elettrolitico in operai affetti da mal dei cassoni. *Acta Neurol.*, Napoli, **1955**, *10*: 879-906.

ANDRÉ-BALISAUX, G. et GONSETTE, R. L'électroencéphalographie dans le somnambulisme et sa valeur pour l'établissement d'un diagnostic étiologique. *Acta neurol. psychiat. Belg.*, **1956**, *56*: 270-281.

ARELLANO, A. P. and JERÍ, V. R. Scalp and basal electroencephalogram during the effect of reserpine. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *75*: 525-533.

BAGCHI, B. K. The progress of electroencephalography. *Trans. Bose Res. Inst.*, Calcutta, **1955**, *20*: 55-65.

BAIRD III, H. W. and GARFUNKEG, J. M. EEG changes in children with artificially induced hyperthermia. *J. Pediat.*, **1956**, *48*: 28-33.

BELLVILLE, J. W., HOWLAND, W. S. and BOYAN, C. P. Comparison of the EEG patterns during steroid and barbiturate narcosis. *Brit. J. Anaesth.*, **1956**, *28*: 50-54.

BERCEL, N. A., TRAVIS, L. E., OLINGER, L. B. and DREIKURS, E. Model psychoses induced by LSD-25 in normals. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *75*: 588-611.

BERGMAN, P. S. and GREEN, M. A. The use of electroencephalography in differentiating psychogenic disorders and organic brain diseases. *Amer. J. Psychiat.*, **1956**, *113*: 27-31.

BERNHARD, C. G. and BOHM, E. The action of local anaesthetics on experimental epilepsy in cats and monkeys. *Brit. J. Pharm. Chemother.*, **1955**, *10*: 288-295.

BISHOP, G. H. Natural history of the nerve impulse. *Physiol. Rev.*, **1956**, *36*: 376-399.

BLUMENTHAL, I. J. Spontaneous seizures and related electroencephalographic findings following shock therapy. *J. nerv. ment. Dis.*, **1955**, *122*: 581-588.

BONNET, M. H. Action des neuroleptiques sur les crises et les troubles mentaux de certains épileptiques. *Ann. méd.-psychol.*, **1956**, *114*: 193-226.

BORNSTEIN, M., CODDON, D. and SONG, S. Prolonged alterations in behavior associated with a continuous electroencephalographic (spike and dome) abnormality. *Neurol.*, **1956**, *6*: 444-448.

BREMER, F. Quelques aspects physiologiques du problème des relations réciproques de l'écorce cérébrale et des structures sous-corticales. *Acta neurol. psychiat. Belg.*, **1955**, *55*: 947-965.

BREMER, F. et STOUPEL, N. Interprétation de la réponse de l'aire visuelle corticale a une volée d'influx sensoriel. *Arch. int. Physiol.*, **1956**, *64*: 234-250.

BROBECK, J. R., LARSSON, S. and REYES, E. A study of the electrical activity of the hypothalamic feeding mechanism. *J. Physiol.*, **1956**, *132*: 358-364.

CANALI, G. e CARPITELLA, A. Rilievi statistici sul ritmo "en arceau". *Sist. Nerv.*, Milano, **1956**, *8*: 8-12.

CANALI, G. e PISANI, C. Reperti elettroencefalografici in 162 casi di idrocefalo atrofico. *Sist. Nerv.*, Milano, **1956**, *8*: 129-141.

CANESTRARI, R. Emisferectomia e funzioni psicomotorie. *Riv. Sperim. Freniatr.*, **1956**, *80*: 319-344.

CATALANO, L. e SERRA, C. Modificazioni dell'attività elettrica cerebrale in un gruppo di pazienti sottoposti a blocco del ganglio stellato. *Acta Neurol.*, Napoli, **1955**, *10*: 853-861.

CAZZULLO, C. L. Sistema nervoso e ibernazione artificiale (Rassegna critica e contributo di neurofisiopatologia sperimentale). *Riv. Sperim. Freniatr.*, **1956**, *80*: 7-105.

COIRAULT, R., DAMASIO, R. et CHAMBON. Quelques considérations sur un stéroïde anesthésique: le succinate sodique de 21 hydroxy-pregnandione (Viadril). *Encéphale*, **1956**, *45*: 81-97.

COIRAULT, R., SCHULLER, E., PERRIER, M. et GUILLARD, A. Utilisation en psychiatrie du C 11 511, nouvel hypnotique non barbiturique. *Presse Méd.*, **1956**, *64*: 986-988.

COLONY, H. S. and WILLIS, S. E. Electroencephalographic studies of 1,000 schizophrenic patients. *Amer. J. Psychiat.*, **1956**, *113*: 163-169.

CROSSLAND, J. and MITCHELL, J. F. The effect on the electrical activity of the cerebellum of a substance present in cerebellar extracts. *J. Physiol.*, **1956**, *132*: 391-405.

DAS, N. N., DASCUPTA, S. R. and WERNER, G. Changes of behaviour and electroencephalogram in rhesus monkeys caused by chlorpromazine. *Arch. int. Pharmacodyn., Gand.*, **1954**, *99*: 451-457.

DAVIDSON, S. and WATSON, G. W. Hereditary light sensitive epilepsy. *Neurol.*, **1956**, *6*: 235-261.

DELAY, J., SCHULLER, E., DROSSOPOULO, G. et VERDEAUX, G. et J. Un nouvel activant des électroencéphalogrammes: l'imide de l'acide éthyl-méthyl glutarique (NP13), ou Mégimide. *Rev. Neurol.*, Paris, **1956**, *94*: 315-318.

DOBKIN, A. B., LAMOUREUX, L. and GILBERT, R. G. B. Physiological effects of chlorpromazine. *Anaesthesia*, **1954**, *9*: 157-174.

DREYER, R. Hirnelektrischer Befund bei einem anatomisch gesicherten Fall von Leukóencephalitis van Bogaert. *Nervenarzt*, **1956**, *27*: 227-228.

EEG and the classification of epilepsy. *Lancet*, **1956**, Vol. I, 946.

ERULKAR, S. D., ROSE, J. E. and DAVIES, P. W. Single unit activity in the auditory cortex of the cat. *Bull. Johns Hopkins Hosp.*, **1956**, *99*: 55-86.

FAETH, W. H., WALKER, A. E. and WARNER, W. A. Experimental subcortical epilepsy. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *75*: 548-562.

FEREY, D. L'Hémisphérectomie cérébrale dans le traitement de l'hémiplégie et de certaines encéphalopathies infantiles. Réflexions à propos de dix cas personnels opérés. *Presse Méd.*, **1956**, *64*: 81-84.

FISCHGOLD, H. et ZALIS, A. Electro-encéphalographie et sécurité routière. *Presse Méd.*, **1956**, *64*: 875-876.

FRANCO, J. y QUEROL, M. La electroencefalografía en las disquinesias. *Rev. neuro-psiquiat.*, **1955**, *18*: 446-461.

FRIEDLANDER, W. J. and FEINSTEIN, G. H. Petit mal status. Epilepsia minoris continua. *Neurol.*, **1956**, *6*: 357-362.

FRIEDMAN, S. B. and ENGEL, G. L. Effect of cortisone and adrenocorticotropin on the electroencephalogram of normal adults: quantitative frequency analyses. *J. Clin. Endocrinol.*, **1956**, *16*: 839-847.

GASTAUT, H., BERNARD, R., NAQUET, R. et WILSON, J. Etude électro clinique quotidienne d'un état confusionnel épileptique simple ayant duré un mois. *Rev. Neurol.*, Paris, **1956**, *94*: 267-272.

GASTAUT, H., PAILLAS, J. et POINSO, R. Localisation anatomique et électroencéphalographique d'une épilepsie temporo-occipitale caractérisée par des crises métamorphosiques avec altération du schéma corporel. *Rev. Neurol.*, Paris, **1956**, *94*: 272-279.

GASTAUT, H., RADERMECKER, J., VIGOUROUX, R. et VAN BOGAERT, L. Une méningoencéphalite suraigüe dans la mononucléose (Etude anatomoclinique et électroencéphalographique). *Rev. Neurol.*, Paris, **1956**, *94*: 23-39.

GASTAUT, H., ROGER, J. et ROGER, A. Sur la signification de certaines fugues épileptiques. A propos d'une observation électroclinique d'"état de mal temporal". *Rev. Neurol.*, Paris, **1956**, *94*: 298-301.

GONSETTE, R. La perméabilité des vaisseaux cérébraux. Nouvelle méthode d'étude: le test encéphalographique de la pénicilline. *Acta neurol. psychiat. Belg.*, **1956**, *56*: 313-322.

GOODDY, W. Cerebral representation. *Brain*, **1956**, *79*: 167-187.

GÖTZE, W. und KOFES, A. Uber Radio-elektrencephalographie. (Eine Methode zum Studium des Einflusses körperlicher Belastungen auf die Hirnfunktion.) *Z. ges. exp. Med.*, **1955**, *126*: 439-443.

GUALTIEROTTI, T. and PATERSON, A. S. The physiological effects of non-convulsive bitemporal stimulation in the baboon and man. *Confinia Neurol.*, **1956**, *16*: 38-64.

GUILLAUME, J. et MAZARS, G. L'Etat de mal cortical. Indications d'un traitement chirurgical d'urgence. *Rev. Neurol.*, Paris, **1956**, *94*: 52-60.

HAMOEN, A.-M., HERNGREEN, H., VAN LEEUWEN, W. S. et MAGNUS, O. Encéphalite subaiguë progressive; constatations cliniques et électroencéphalographiques dans 23 cas. *Rev. Neurol.*, Paris, **1956**, *94*: 109-119.

HIEBEL, G., BONVALLET, M. and DELL, P. Action de la chlorpromazine (Largactil 4560 RP) au niveau du système nerveux central. *Sem. hôp.*, Paris, **1954**, *30*: 2346-2353.

INGHIRAMI, L. e MURATORIO, A. L'EEG nel parkinsonismo. *Riv. Neurobiol.*, **1955**, *1*: 403-431.

JUS, A. and JUS K. [Bioelectric researches on the formation and transformation of conditioned motor reflexes in the dynamic stereotype. Report III.] *Neurol. Neurochir. Psychiat. Polska*, **1956**, *6*: 291-311.

JUSOWA, K., KUBERSKI, Z., MARGOLISOWA, A., RADZIKOWSKA, H. [Electroencephalographic and neurological evaluation of therapeutic results obtained in tuberculous meningo-encephalitis in children]. *Neurol. Neurochir. Psychiat. Polska*, **1956**, *6*: 143-169.

KENNARD, M. A., RABINOVICH, M. S., SCHWARTZMAN, A. E. and FISTER, W. P. Factor of aggression as related to the electroencephalogram. *Dis. nerv. Syst.*, **1956**, *17*: 127-131.

KING, E. E. Differential action of anesthetics and interneuron depressants upon EEG arousal and recruitment responses. *J. Pharm. exp. Ther.*, **1956**, *116*: 404-417.

KOPELOFF, L. M., CHUSID, J. G. and KOPELOFF, N. Convulsant effects of semi-carbazide in epileptic monkeys. *Proc. Soc. exp. Biol.*, N. Y., **1956**, *92*: 132-134.

KREINDLER, A., VOICULESCO, V., BROSTEANU, R., VOINESCO, I. et NESTIANU, V. Recherches électrocérébrographiques sur l'accès convulsif expérimental. *Rev. Neurol.*, Paris, **1956**, *94*: 120-135.

KUBICKI, ST. Uber EEG und cerebralen Kompensationsgrad bei Hirntumorkranken. *Dtsch. Z. Nervenheilk.*, **1955**, *174*: 42-50.

LAFON, R. et LABAUGE, R. Le devenir des encéphalopathies de l'enfant. *Montpellier Med.*, **1956**, *49*: 25-55.

LAFON, R., PASSOUANT, P., FAURE, J.-L. et MINVIELLE, J. Epilepsie et gémellite (étude clinique, électroencéphalographique et psychologique de 7 couples de jumeaux univitellins épileptiques). *Montpellier Méd.*, **1956**, *49*: 56-75.

LEIGH, D. and POND, D. A. The electroencephalogram in cases of bronchial asthma. *J. Psychosomat. Res.*, **1956**, *1*: 120-127.

LI, C. The inhibitory effect of stimulation of a thalamic nucleus on neuronal activity in the motor cortex. *J. Physiol.*, **1956**, *133*: 40-53.

LONGO, V. G., VON BERGER, G. P. and BOVET, D. Action of nicotine and of the "gangliоplegiques centraux" on the electrical activity of the brain. *J. Pharm. exp. Ther.*, **1954**, *3*: 349-359.

LUNDERVOLD, A. and SKATVEDT, M. Migration of spike foci from one hemisphere to the other in children. *J. Pediat.*, **1956**, *48*: 457-464.

MCINTYRE, A. K., MARK, R. F. and STEINER, J. Multiple firing at central synapses. *Nature*, **1956**, *178*: 302-304.

MARIA, G. Ricerche elettroencefalografiche nel pavor nocturnus. *Cervello*, **1956**, *32*: 101-112.

MEURICE, E. Compte rendu du colloque de Marseille sur l'EEG et les phénomènes psychologiques. *Acta neurol. psychiat. Belg.*, **1956**, *56*: 253-263.

MEYER, J. S., LEIDERMAN, H. and DENNY-BROWN, D. Electroencephalographic study of insufficiency of the basilar and carotid arteries in man. *Neurol.*, **1956**, *6*: 455-477.

MIHAILOVIC, L. and DELGADO, J. M. R. Electrical stimulation of monkey brain with various frequencies and pulse durations. *J. Neurophysiol.*, **1956**, *19*: 21-36.

MOND, W. Ein Index zur Bestimmung der Stabilität des Wellenablaufes in der Occipitalableitung beim EEG. *Mschr. Psychiat. Neurol.*, **1955**, *129*: 411-418.

MONTANARI, M. e ROMERIO, C. Considerazioni su alcum aspetti elettroencefalografici nelle sindromi vasali acute intracraniche. *Rass. stud. psichiat.*, **1956**, *45*: 57-91.

MORRELL, F. Interseizure disturbances in focal epilepsy. *Neurol.*, **1956**, *6*: 327-334.

MUNDY-CASTLE, A. C. The electroencephalogram in relation to temperament. *Acta Psychol.*, **1955**, *11*: 397-411.

MUNDY-CASTLE, A. C. The EEG in twenty-two cases of murder or attempted murder. Appendix on possible significance of alphoid rhythms. *J. Nat. Inst. Personnel Res.*, **1955**, *6*: 103-120.

MUNDY-CASTLE, A. C. The relationship between primary-secondary function and the alpha rhythm of the electroencephalogram. *J. Nat. Inst. Personnel Res.*, **1955**, *6*: 95-102.

NEGRI, S. Considerazioni sull'elettroencefalogramma dei tumori della fossa posteriore e del terzo ventricolo. *Sist. Nerv.*, Milano, **1955**, *7*: 336-358.

OLDS, J. A preliminary mapping of electrical reinforcing effects in the rat brain. *J. comp. Physiol. Psychol.*, **1956**, *49*: 281-285.

PAPEZ, J. W. Path for projection of non-specific diffuse impulses to cortex for EEG. related to conciousness. *Dis. nerv. Syst.*, **1956**, *17*: 103-108.

PETSCHE, H., MARKO, A. und MONNIER, M. Mikrozeitliche toposkopische Analyse bioelektrischer Hirnwellen beim Kaninchen. I. Die Ausbreitung der Spontantätigkeit und elektrisch ausgelöster Entladungen am Cortex. *Helvet. physiol. pharm. Acta.*, **1955**, *13*: 354-371.

POSTEL, J. et COSSA, P. La thérapeutique par la psychose induite (mescaline et chlorpromazine). *Ann. med.-psychol.*, **1956**, *114*: 254-282.

Progress in electroencephalography: international meeting in London. *Brit. med. J.*, **1956**, No. 4980, 1423.

QUEROL, M. El electroencefalograma en un grupo de sujetos normales. *Ann. Fac. med.*, Lima, **1956**, *39*: 288-301.

ROSSINI, R., REGGIANI, R. e ZANOCCO, G. Le sindromi atrofiche cerebrali. (Studio clinico, neuroradiologico, elettroencefalografico). *Riv. Patol. nerv. ment.*, **1955**, *76*: 1-95.

SALMON, H. A. Case of hypopituitary coma with serial electroencephalography. *Brit. med. J.*, **1956**, No. 4980, 1397-1399.

SATO, K. A new practical method for obtaining the number of the components in the electroencephalogram. *Folia Psychiat. Neurol. Jap.*, **1956**, *9*: 309-313.

SCHAEFER, J. und KUBICKI, ST. Uber eine vereinfachte Methodik epiduraler Ableitungen im Tierversuch unter Berücksichtigung histo-pathologischer Untersuchungen. *Z. ges. exp. Med.*, **1955**, *127*: 22-29.

SCHWARZ, B. E., BICKFORD, R. G. and RASMUSSEN, W. C. Hypnotic phenomena, including hypnotically activated seizures, studied with the electroencephalogram. *J. nerv. ment. Dis.*, **1955**, *122*: 564-574.

SCHWARZ, B. E., SEM-JACOBSEN, C. W. and PETERSEN, M. C. Effects of mescaline, LSD-25, and adrenochrome on depth electrograms in man. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *75*: 579-587.

SERRA, C. e DE NATALE, L. Sul valore della idratazione pitressinica comme prova di attivazione dell'elettroencefalogramma. *Acta Neurol.*, Napoli, **1955**, *10*: 907-915.

SHAGASS, C. Clinical neurophysiological studies of affect. *Amer. J. Psychiat.*, **1956**, *112*: 928-930.

SILVER, M. L. Intracranial surgery for hemiplegia and convulsions. *Rhode Island med. J.*, **1956**, *39*: 251-256.

SINISI, L. Contributo alla conoscenza dell'azione della reserpina sul sistema nervoso. *Neuropsichiat.*, Genova, **1956**, *12*: 45-54.

SLOCOMBE, A. G., HOAGLAND, H. and TOZIAN, L. S. Effects of certain indole amines on electrical activity of the nervous system. *Amer. J. Physiol.*, **1956**, *185*: 600-606.

SOILLE, P. L'hématome intracérébral chronique. *Acta neurol. psychiat. Belg.*, **1956**, *56*: 188-205.

STREIFLER, M. and LANDAU, J. Electrical brain potentials in retinitis pigmentosa and familial hemeralopia. *Ophthalmologica*, Basel, **1955**, *130*: 117-127.

STROBOS, R. R. J. The temporal lobe. *Folia Psychiat. Neerl.*, **1956**, *59*: 142-170.

SZATMARI, A. Clinical and electroencephalogram investigation on largactil in psychosis (preliminary study). *Amer. J. Psychiat.*, **1956**, *112*: 788-794.

TURNER, M. La electroencefalografía en psicología y psiquiatría. *Acta Neuropsiq.*, Argentina, **1955**, *1*: 401-410.

TURNER, M. y TURNER, N. Caracteres electrográficos de la epilepsia en flexión generalizada. *Arch. Argent. Pediat.*, **1955**, *43*: 280-288.

VAN WULFFTEN PALTHE, P. M. Aspects biologiques de l'électro-encéphalographie. *Méd. Aéronaut.*, **1956**, *11*: 45-54.

VERZEANO, M. Activity of cerebral neurons in the transition from wakefulness to sleep. *Science*, **1956**, *124*: 366-367.

VERZEANO, M. Sequential activity of cerebral neurons. *Arch. int. Physiol.*, **1955**, *63*: 458-476.

WAKOH, T. A case of precocious puberty with epileptic seizure. *Folia Psychiat. Neurol. Jap.*, **1956**, *9*: 329-340.

WEIL, A. A. Ictal depression and anxiety in temporal lobe disorders. *Amer. J. Psychiat.*, **1956**, *113*: 149-157.

WEIL, A. A. and NOSIK, W. A. Electrophysiologic and clinical observations in hemifacial spasms. *Neurol.*, **1956**, *6*: 381-389.

WIKLER, A., PESCOR, F. T., FRASER, H. F. and ISBELL, H. Electroencephalographic changes associated with chronic alcoholic intoxication and the alcohol abstinence syndrome. *Amer. J. Psychiat.*, **1956**, *113*: 106-114.

WILLIAMS, D. The structure of emotions reflected in epileptic experience. *Brain*, **1956**, *79*: 29-67.

YAHR, M. D. and MERRITT, H. H. Current status of the drug therapy of epileptic seizures. *J. Amer. med. Ass.*, **1956**, *161*: 333-338.

YOSHII, N. Methodological principles of electroencephalographic investigation on conditioned behavior. *Folia Psychiat. Neurol. Jap.*, **1956**, *9*: 341-365.

ZIMMERMAN, F. T. Evaluation of N-Methyl-A, A-Methylphenyl succinimide in the treatment of petit mal epilepsy. *N. Y. St. J. Med.*, **1956**, *56*: 1460-1465.

ZIMMERMAN, F. T. Explosive behavior anomalies in children on an epileptic basis. *N. Y. St. J. Med.*, **1956**, *56*: 2537-2543.

ZIMMERMAN, F. T. N-methyl-a, a-methylphenyl succinimide in psychomotor epilepsy therapy. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *76*: 65-71.

Contents

FOR NOVEMBER 1956

	Page
Measurement of the depth of barbiturate narcosis, by ALEXANDER FORBES, M.D., JEROME K. MERLIS, M.D., GEORG F. HENRIKSEN, M.D., SYLVIA BURLEIGH, JEANNETTE H. JIUSTO and GRACE L. MERLIS	541
Thalamic control of certain normal and abnormal cortical rhythms, by B. RALSTON, M.D. and C. AJMONE-MARSAN, M.D.	559
Potential wave mechanisms in cat cortex, by M. H. CLARE, M.A. and G. H. BISHOP, Ph.D.	583
Studies of the adrenaline-sensitive component of the reticular activating system, by ALAN BURNS ROTHEALLER, M.D.	603
Electrographic aspects of an "arousal" or attention reaction induced in the unanesthetized rabbit by the presence of a human being, by H. GANGLOFF and MARCEL MONNIER	623
The relation between the startle reaction and the non-specific EEG response to sudden stimuli with a discussion on the mechanism of arousal, by LARS-ERIK LARSSON	631
Developmental study of the electroencephalogram of the dog, by MARGARET S. CHARLES, M.S. and JOHN L. FULLER	645
Frequency of photic stimulation as a variable in the activation of experimental convulsions, by KENNETH A. KOOI, M.D. and EDWARD C. BECK, Ph.D.	653
CLINICAL AND LABORATORY NOTES :	
Unusual EEG in unconscious patient with brain stem atrophy, by ARNE LUNDERVOLD, M.D., TORMOD HAUGE, M.D. and AAGOT C. LÖKEN, M.D.	665
Effects of chlorpromazine on the electroencephalogram with report of a case of chlorpromazine intoxication, by JENNIE MAUCERI M.D. and HANS STRAUSS, M.D.	671
Pontine or "reticular" epilepsy: report of a case, by CH. ARAKI, M.D., K. SAKATA, M.D. and T. KUROKI	676
EEG changes in amyotrophic lateral sclerosis, by WALTER J. FRIEDLANDER, M.D.	678
Loss of right hemisphere due to natural causes, by STUART WEISS, M.D., IRWIN LEVY, M.D., DAVID SMITH, M.D. and JAMES O'LEARY, M.D.	682
TECHNICAL NOTES :	
A simple anti-blocking device, by CARL BAUMANN, BIRGER R. KAADA, M.D. and KRISTIAN KRISTIANSEN, M.D.	685
Another simple method for the simultaneous cinematographic recording of the patient and his electroencephalogram during seizures, by L. F. STEWART, M.D., H. H. JASPER, M.D. and C. HODGE, M.D.	688
Storage of silver chloride electrodes, by R. COOPER, Ph.D.	692
A coupling circuit for the Bickford integrator, by JOHN DEGELMAN	693
Deux procédés de modulation de luminosité du spot pour l'oscillographie cathodique de potentiels bioélectriques, par JEAN CERF, M.D. and CHARLES LIBERT	695
SOCIETY PROCEEDINGS	699
BOOK REVIEWS	736
INDEX TO CURRENT LITERATURE	741
ANNOUNCEMENTS	622, 630, 664
ERRATUM	664

Copyright by the Editors

REPRINTED IN THE NETHERLANDS

TITLE: ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY.

VOLUME: 9

DATE: 1957

CONTROL NO: 30

NOTES:

SCIENTIFIC, TECHNICAL AND MEDICAL JOURNALS IN MICROFORM

This microform is part of the MICROFORM PROGRAMME of back volumes covering the ELSEVIER – NORTH HOLLAND – EXCERPTA MEDICA imprints.

Over 400 titles are now available on 16 mm or 35 mm – positive or negative – film from Volume 1 to the last complete subscription year.

All microform is produced on polyester-base silver halide film and conforms to international standards of archival quality.

© ELSEVIER SEQUOIA S.A. 1977 and subsequent years.

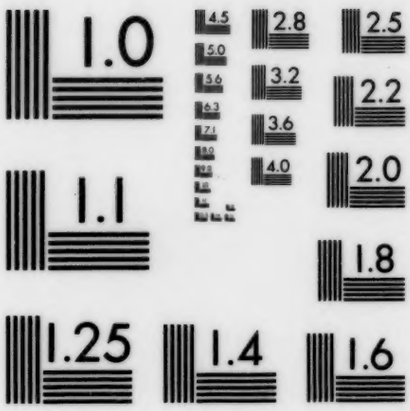
All rights reserved. No part of this microform may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the microform publishers: Elsevier Sequoia S.A., P.O. Box 564, 1001 Lausanne 1, Switzerland.

For further information on the complete microform programme of the ELSEVIER – NORTH HOLLAND – EXCERPTA MEDICA journals contact your dealer, agent or the micropublishers:

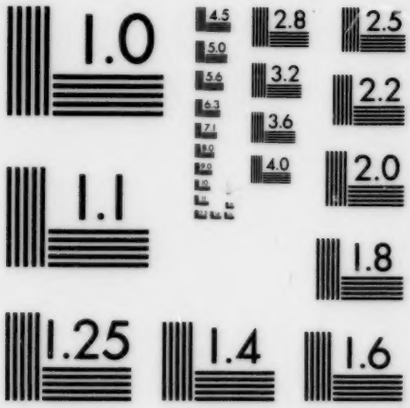
ELSEVIER SEQUOIA S.A.
Special Services Department
P.O. Box 564
1001 Lausanne 1, Switzerland
Telephone: (21) 20 73 81
Telefax: (21) 235-444
Telex: 26 620 ELSA CH

North American customers may also contact:

ELSEVIER SCIENCE PUBLISHING COMPANY, INC.
Journal Information Center
52 Vanderbilt Avenue
New York, NY 10017, U.S.A.
Telephone: (212) 876 9040
Telefax: (212) 916 12 1288
Telex: 420 643 AEP UI


1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
4.5
5.0
5.6
6.3
7.1

0 cm
5 cm
10 cm


1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
4.5
5.0
5.6
6.3
7.1